Prevention of Major Amputation secondary to Diabetes-related Foot Disease

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SUMMARY

Incidence of amputation secondary to diabetic foot disease is unacceptably high, especially as up to 80% of these amputations are deemed preventable through optimal management and education. Tackling complications and reducing amputation rates requires a holistic approach identifying issues at a person, system and population level. Investing in preventive strategies is cost effective and avoids the burden of extremely costly reactive interventions. The overarching aim of this thesis was to understand the previously undocumented burden of diabetes-related amputation and the associated risk factors for amputation within Wales. The thesis investigated amputation rates and mortality in the Welsh population with and without diabetes over the last decade for both major and minor amputations using a repository of medical data of all Welsh residents. The thesis also examined risk factors for amputation at a person, health board and population level using different methodologies to quantify specific risks. This included root cause analysis to assess care provision and questionnaires to understand patient's knowledge and behaviours. The thesis identified variance from gold standards of care for diabetic foot disease and most amputations in the root cause analysis were determined potentially preventable. However, it identified simple behavioural and educational measures and areas for implementation of risk reduction strategies within our health board. Despite the population with diabetes representing only 7% of the total Welsh population, they accounted for over 50% of the incident amputations performed. Only a minor reduction in rate of amputation was seen over time and there was marked variance in rates between health boards. Mortality following major amputation was high with a mortality rate of 61.9% at 5 years in the total population and 67% in the population with diabetes. By highlighting variance and current trends in care the thesis provides the grounds for the implementation of interventions to reduce amputation rates.

DECLARATIONS AND STATEMENTS

DECLARATION

This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree.

Signed . [redacted]..... (candidate)

Date 18/08/2021.....

STATEMENT 1

This thesis is the result of my own investigations, except where otherwise stated. Where correction services have been used, the extent and nature of the correction is clearly marked in a footnote(s).

Other sources are acknowledged by footnotes giving explicit references. A bibliography is appended.

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STATEMENT 2

I hereby give consent for my thesis, if accepted, to be available for photocopying and for inter-library loan, and for the title and summary to be made available to outside organisations.

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Date 18/08/2021.....

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LIST OF ABBREVIATIONS

AB	Aneurin Bevan Health Board
ABMU	Abertawe Bro Morgannwg University Health Board
ABPI	Ankle brachial pressure index
ACE	Angiotensin-converting enzyme
ADBE	Annual district birth extract
ADDE	Annual district death extract
ADMA	Asymmetric dimethylarginine
AGEs	Advanced glycation end products
AKA	Above Knee Amputation
ALF	Anonymised linking field
ARB	Angiotensin II receptor blocker
Ard	Amputation rate in the population with diabetes
Arn	Amputation rate in the population without diabetes
Art	Amputation rate in the total population
ATMs	Adipose tissue macrophages
AV	Arterial-venous
BASIL	Bypass versus Angioplasty in Severe Ischaemia of the Leg
BC	Betsi Cadwaladr Health Board
BKA	Below knee amputation
BMI	Body Mass index
C&V	Cardiff & Vale Health Board
CAD	Coronary Artery Disease
CAN	Cardiac Autonomic Neuropathy
CCF	Congestive cardiac failure
CCGs	Clinical Commissioning Groups
CED	Cause and effect diagram
CI	Confidence intervals
CLI	Critical Limb Ischaemia
CRP	C-reactive Protein
CT	Cwm Taff Local Health Board
CTA	CT angiogram
CV	Cardiovascular
CVA	Cerebrovascular accident
DKA	Diabetic ketoacidosis
DKT	Diabetes Knowledge test
DNA	Did not attend
DSN	Diabetes Specialist Nurse
DSR	Direct standardised rates
ER	Endoplasmic reticulum
ESR	Erythrocyte sediment rate
ESRD	End stage renal disease

EUCLID	cardiovascular Effects of Ticagrelor and Clopidogrel in Patients with Peripheral Artery Disease
FFA	Free fatty acids
G6PD	Glucose-6-phosphate dehydrogenase
GI	Gastrointestinal
GLEAS	Global Lower Extremity Amputation Study
GP	General Practitioner
HB	Health Board
HbA1c	Haemoglobin A1c
HD	Hywel Dda.
HDL	High-density lipoprotein
HES	Hospital Episode Statistics
HTN	Hypertension
ICD10	International Classification of Diseases 10
IDF	International Diabetes Federation
IGF	Insulin-like growth factor
il-1	Interleukin-1
IL-1β	Interleukin 1β
IQR	Interquartile range
IWGDF	International Working Group on the Diabetic Foot
LADA	Latent Autoimmune Diabetes in Adults
LDL	Low-density lipoprotein
LSOA	Lower super output areas
MAPK	Mitogen-activated protein kinase
MDT	multidisciplinary team
MI	Myocardial infarction
MODY	Maturity onset diabetes of the young
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant Staphylococcus aureus
NADPH	Nicotinamide adenine dinucleotide phosphate
NAFF	Nottingham Assessment of functional footcare
NASH	Non-alcoholic steatohepatitis
NF-kB	Nuclear factor Kappa-light-chain-enhancer of activated B cells
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPSA	National Patient Safety Agency
NWIS	NHS Wales Informatics Service
OM	Osteomyelitis
ONS	Office of National Statistics
OPCS4	Office of Population, Census and Surveys interventions and procedures version 4
OPDW	Outpatient Database for Wales
OR	Odds Ratio

PEDW	Patient Episode Database for Wales
PHE	Public Health England
PKC	Protein kinase c
PVD	Peripheral Vascular Disease
PY	person years
QOF	Quality and Outcomes Framework
R5P	Ribose 5-phosphate
RAAS	Renin-Angiotensin-Aldosterone system
RAGE	Receptor for Advanced Glycation Endproducts
RCA	Root Cause Analysis
RCS	Royal College of Surgeons
Redox	Reduction-oxidation
RRT	Renal replacement therapy
SAIL	Secure Anonymised Information Linkage Databank
SBP	Systolic BP
SINBAD	Site, Ischaemia, Neuropathy, Bacterial Infection and Depth score
SM	Skeletal muscle
T1DM	Type 1 Diabetes
TBPI	Toe brachial pressure index
TcPO2	Transcutaneous oxygen pressure
TLR	Toll like receptor
TNF-α	Tumour necrosis factor-α
UK	United Kingdom
UKPDS	UK Prospective Diabetes Study
WBC	White Blood Cell count
WCC	White Cell Count
WCP	Welsh Clinical Portal
WDSD	Welsh Demographic Service Database
WHO	World Health Organisation
WIMD	Welsh Index of multiple deprivation
WLGP	Welsh Longitudinal General Practice database
WOB	Week of birth

CONFERENCE PROCEEDINGS

Hayes, J.,Thomas, R.,Hickey, B.,Price.D.,Ferguson.C.,Bain,S.,Topliss,C.,Stephens,J. Root cause analysis of major lower limb amputations: How can we reduce rates? National Poster Presentation. Diabetes UK Professional Conference 2019, ACC Liverpool, Liverpool,6-8th March 2019.

Hayes,J.,Stephens,J.,Bain,S., Topliss,C.,Thomas,.R.,Price,D. Is social deprivation associated with amputation risk secondary to diabetic foot disease? National Poster Presentation. Diabetes UK Professional Conference 2018, London ExCeL, London, 14-16th March 2018. Nominated for Lilly Diabetes Clinical Science Poster Award

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REPORTS

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Presented at -

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CHAPTER ONE

INTRODUCTION AND REVIEW OF LITERATURE

1.1 Overview

The most recent National Institute for Health and Care Excellence (NICE) guidelines 'Diabetic Foot Problems: Prevention and Management' have highlighted that levels of morbidity and mortality related to diabetes-related foot disease throughout the UK are at an unacceptably high level. Foot related complications create a significant burden on patients, the National health service (NHS) and the United Kingdom (UK) economy and there is a marked variation in their incidence across regions (NICE, 2016). Foot problems, ranging from ulceration to amputation, account for the highest proportion of hospital admissions for any long-term micro or macrovascular complication of diabetes (NHSWales, 2016). Amputations secondary to diabetes-related foot disease within the UK are intolerably high (NICE, 2016) where up to 80% of amputations in persons with diabetes are felt to be preventable through optimal management and education (Diabetes UK, 2015c). However, despite advances in patient care and education, the number of amputations secondary to diabetes related foot disease is rising (Diabetes UK, 2018). With the rising prevalence of diabetes and age distribution shifts, crude rates of amputation are expected to increase further. The cost of amputation to the NHS will soon become overwhelming, due high procedural costs, expensive supplementary care and the loss to the working adult population.

The impact on morbidity and associated mortality for people with diabetes where foot disease progresses to the point of amputation is substantial (NICE, 2016). In people with diabetes, the median survival after amputation of any cause has been reported to be 20 months shorter compared to people without diabetes (Fortington et al., 2013). Five-year mortality rates after amputations in people with diabetes are reported to be as high as 80% (Diabetes UK, 2015c). Even in those who develop foot ulceration but do not progress to amputation there is an approximate twofold increased risk of premature death (Scott et al., 2014). As well as the cost to the individual and their quality of life, the financial burden of amputations on a health board is considerable with the primary treatment episode of major lower limb amputation being approximately í40,000 (NICE, 2016).

It is estimated that every 20 seconds an amputation secondary to diabetic foot disease occurs somewhere in the world (International Working Group on the diabetic foot, 2019). However, there is variance in the incidence of amputation across and within countries including within the UK. National data shows up to a fourfold variance in the amputation rate throughout the regions of England (Holman, Young, & Jeffcoate, 2012) and differences in amputation incidence have been reported in Scotland and Ireland. Within Wales, from data of crude amputation rates there seems to be variance in the number of amputations performed within the diabetes population by health board. This is particularly evident within the Swansea locality (NWIS, 2017). This does not appear to be due to a higher incidence of diabetes and it is unclear at present what factors are responsible for driving this variance.

Diabetes results in amputation through three common processes, peripheral vascular disease, neuropathy and subsequent infection of the foot. These are all secondary to vascular dysfunction and endothelial damage resulting from the effects of high glucose on tissues. The long term marco and micro vascular complications associated with hyperglycaemia are thought to be preventable if affective intervention is made early in the disease course (Laiteerapong et al., 2019). Tackling the complications of diabetes and ultimately reducing amputation rates requires a holistic approach identifying issues at a person, healthcare system and population level. The person with diabetes also needs to be approached comprehensively, addressing the full burden of disease along with consideration of socioeconomic and psychological issues. First problems must be identified and then issues must be reviewed through a holistic approach looking at the whole population and whole person, involving the full healthcare system from health board to patient education.

As variance in amputation rates are seen between and within countries the first step in addressing these issues is to accurately identify the amputation rates within a population and then identify inequalities within it. Once inequalities are identified, these can be explored further to inform strategies to change practice. As addressing amputation requires a holistic approach, so does addressing inequalities between health boards. At present there is no published data on

diabetes-related amputations in Wales. The thesis aims to obtain a better understanding of the current situation in Wales through providing accurate epidemiological data and exploring amputation at a population, health board and person level to identify inequalities and ultimately inform preventative strategies.

1.2 Diabetes

Diabetes mellitus is a group of disorders classified by a raised plasma glucose level secondary to a derangement of glucose metabolism. This is the consequence of a relative or complete insulin resistance in cells or an absolute or relative reduction in insulin secretion. Genetic and environmental risk factors act in synchrony to produce a derangement of beta-cell mass or function culminating in a reduction in response to insulin requirements low enough to induce hyperglycaemia (Skyler et al., 2017). Globally, the most prevalent type of diabetes is type 2 (T2DM), affecting 90% of the population with diabetes in the UK (Diabetes UK, 2019b). This is followed by type 1 diabetes (T1DM), affecting around 8% of the population with diabetes and latent autoimmune diabetes in adults (LADA). LADA shares characteristics with both type 1 and 2 diabetes and is the most frequently occurring type of adult onset auto-immune diabetes (Pozzilli at al, 2018). Around 2% of the population have rare, usually genetically predisposed types such as maturity onset diabetes of the young (MODY). Diabetes care as a whole is estimated to account for 10% of all NHS expenditure.

Diabetes is a chronic disorder with multisystem involvement. All forms of diabetes are at the risk of the same complications once hyperglycaemia occurs (Skyler et al., 2017). Complications commonly involve the eye, kidney, heart and foot with diabetic foot disease being the most expensive of all diabetic complications, costing the NHS an estimated í1 in every £100 of all services (M. Kerr, 2019). This expenditure is greater than the estimated expenditure on the common cancers (breast, prostate, and lung cancer) combined (M. Kerr et al, 2019). Diabetic foot disease is also associated with considerable morbidity, mortality and

economic cost secondary to substantial loss of adult working year (International Working Group on the diabetic foot, 2019)

1.2.1 The burden of diabetes

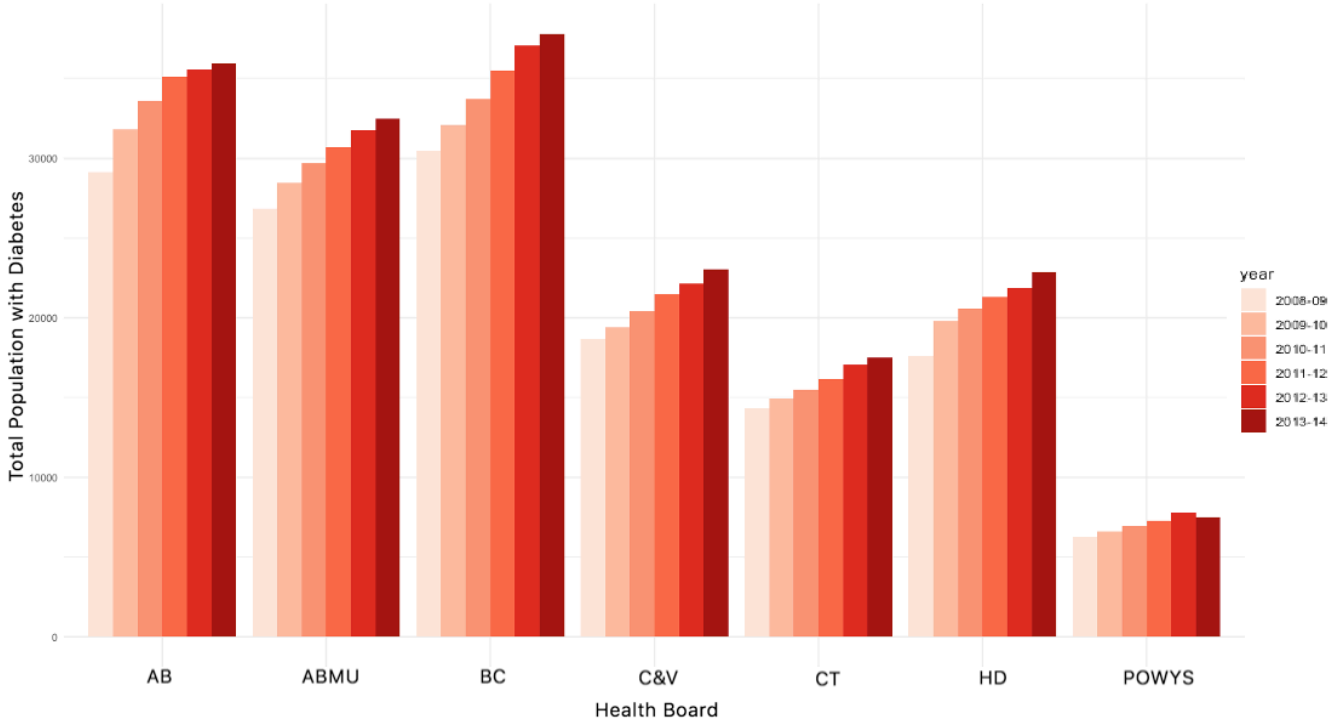
Diabetes is a global epidemic, affecting approximately 463 million adults worldwide (International Working Group on the diabetic foot, 2019). It is the fourth leading cause of mortality within the UK and rates of the disease are steadily increasing secondary to obesity, an ageing population, urbanisation of populations and genetic susceptibility (Paneni, Beckman, Creager, & Cosentino, 2013). In 2013 the World Health Organisation (WHO) set a globally agreed target to halt the raising rate of diabetes by 2025. Most countries, including the UK are not projected to meet this target (WHO, 2016). A rise in rates has been seen in both T1DM and T2DM populations. In 2019 approximately 463 million adults (20-79 years) were living with diabetes; by 2045 this is expected to rise to 700 million, with prevalence rising from 4.7 to 8.5% in adults over 18 (WHO, 2020).

The proportion of people with T2DM as a total proportion of the population with diabetes is increasing as there is a markedly greater rate of change in prevalence when compared to other diabetes types. This is true both worldwide and within the UK (International Diabetes Federation, 2019). This is due to an ageing population combined with a rise in common risk factors for T2DM; obesity, physical inactivity and poor diet. This has led to an increasing overall disease burden along with a rising rate of diagnosis in patients under 40 years of age, and unfortunately, along with diabetes' associated complications. The prevalence of diabetes within UK has more than doubled within the last 20 years increasing to an estimated prevalence of 4.7 million people in 2019 (Diabetes UK, 2019b). This number is expected to rise to greater than 5.5 million by 2030, well beyond the WHO target.

Within Wales the prevalence of diabetes, it's risk factors and its complications are high. Sixty three percent of the population of South Wales are overweight or obese (Public Health Wales, 2019), this is associated with a fourfold risk of diabetes (Barnes, 2011). This is reflected in the

diabetes prevalence in Wales being greater than that seen in the rest of the UK nations (Diabetes UK, 2019b). 7.1% of people over the age of 17 are living with diabetes in Wales compared to 6.4% in England and 5.6% Northern Ireland. Data requested from the National Wales informatics Service (NWIS) looking at diabetes prevalence in Wales in the last six years shows a steady increase in the prevalence of diabetes within every health board as shown in Figure 1.1.

Figure 1.1 Diabetes population changes across Welsh Health Boards from 2008-2014



Data adapted from NWIS, accessed 04/08/2017 (NWIS, 2016); AB :Aneurin Bevan; ABM: Abertawe Bro Morgannwg; BC: Betsi Cadwaladr; C&V: Cardiff & Vale; CT: Cwm Taff; HD: Hywel Dda

There is also a large proportion of patients with undiagnosed diabetes. An estimated 50% of people with diabetes worldwide are undiagnosed (International Diabetes Federation, 2019). With complications of diabetes developing secondary to a period of uncontrolled hyperglycaemia, late diagnosis is associated with a greater risk of complications and will play a large part in the burden of complications in the future (Harris & Eastman, 2000).

1.2.2 The cost of diabetes

A diagnosis of diabetes comes with an associated increase in medical care needs, a reduction in quality of life, an increased risk of hospital admission, stressors on the person and family and ultimately an increased chance of premature death than in those without diabetes (International Diabetes Federation, 2019). These costs increase if a person goes on to develop complications.

The economic costs associated with diabetes on a health service are great. As stated above, diabetes care as a whole is estimated to account for 10% of all NHS expenditure and worldwide 8.3% of all global health care spending is for diabetes, over 150 billion USD (International Diabetes Federation, 2019). Within Wales £500 million, 10% of the annual budget, is spent by NHS Wales on diabetes care. Eighty percent of which goes to managing preventable complications of the disease (Diabetes UK, 2019a). Globally the direct costs related to diabetes were estimated to be 760 billion in 2019 (International Diabetes Federation, 2019). As well as the direct cost to a health care system the cost to the economy is large. One out of four people with diabetes are of working age. This results in a substantial loss of productivity associated with loss of the labour force, early mortality, absenteeism and presenteeism. This is exacerbated when a person progresses to develop complications.

The greatest cost to patients is premature death (Roglic et al., 2005). Annually, 4 million people globally between the age of 20-79 years are expected to die prematurely secondary to diabetes. Forty six percent of those are expected to be within the working age group under 60 years of age (International Diabetes Federation, 2019). Diabetes is responsible for 146,200 deaths annually in the European population under 60 years of age. Within the UK the mortality associated with type 1 diabetes in young people is higher than that seen in the rest of Europe (Ward, Wolfe, & Viner, 2020). Cardiovascular disease is responsible for the greatest mortality in the population with diabetes (Gerstein, 2015) and diabetes doubles the risk of cardiovascular mortality over a person's lifetime (Li, Wang, Zhang, Li, & Liu, 2019). Diabetes also increases the mortality risk due

to chronic respiratory diseases, influenza and pneumonia and renal disease (Li et al., 2019; Morgan, Currie, & Peters, 2000).

1.2.3 The pathogenesis of diabetes

1.2.3.1 Insulin

Insulin is an anabolic peptide hormone produced in the pancreatic islets by beta cells. It is a key hormone in glucose homeostasis, primarily allowing the transport of glucose into cells, along with roles in the metabolism of protein and fat. In both T1DM and T2DM there is a lack of or lack or response to insulin leading to hyperglycaemia.

1.2.3.2 Type 1 diabetes mellitus

In T1DM there is an autoimmune reaction against the beta cells of the pancreatic islets eventually leading to their destruction and an absolute loss of insulin production (Dahlquist, 2006). T1DM is a polygenetic disease with a number of common gene variants that contribute to overall disease risk. It is believed that a genetic susceptibility works in combination with environmental triggers such as a viral infection to precipitate disease onset. The greatest risk is through inheriting a gene variant, the most common of which is a gene variant of human leukocyte antigen (HLA). The genes in HLA are reported to account for approximately 50-60% of genetic risk (Noble et al., 2010), with variance of HLA-DRB1, DQb1 and b*39 locus responsible for 40-50%. An estimated 50 other gene variants contribute a smaller amount (Rich, 1990). In combination these gene variants account for 80% of hereditability of T1DM (Forbes & Cooper, 2013).

Globally, an annual 2-4% increase in incidence of T1DM has been reported (International Diabetes Federation, 2019). As in T2DM, an increase in insulin resistance secondary to obesity can contribute to disease burden. This is often compounded by exogenous insulin which

contributes to weight gain (Dahlquist, 2006). Toxins and dietary factors have been implicated as environmental triggers for developing T1DM. Dietary factors including rapid weight gain and poor infant diet may explain the increase in incidence of T1DM in tandem with T2DM with the increasing prevalence of obesity (Hamman et al., 2014).

1.2.3.3 Type 2 diabetes mellitus

The pathogenesis of T2DM is multifactorial and not yet fully understood. Hyperglycaemia is instigated by an inability of peripheral cells to respond to insulin, a process called insulin resistance. A person at this stage will have an impaired glucose tolerance; a high level of glucose in the blood for a prolonged period after a meal, or an impaired fasting glucose level; a high level of glucose in the blood without a meal but not to the level of diagnosis of T2DM. This resistance drives an increase in insulin production. The increase in insulin production cannot be maintained and eventually this leads to a mismatch between production capacity and demand. The reduction in insulin sensitivity is greatest in skeletal, hepatic and adipose tissues. Ultimately, there needs to be a decrease in secretion of insulin for progression to T2DM to occur.

There is lipid dysregulation in insulin resistance, secondary to a reduced uptake of glucose within the liver. In the liver glucose uptake is triggered by insulin and results in glucose storage as glycogen and downregulation of gluconeogenesis, reducing glucose production and mobilisation of free fatty acids (FFA) from the liver for storage in adipose tissues (Forbes & Cooper, 2013). The perceived low glucose levels within hepatic tissue in insulin resistance result in an increase in insulin release and hepatic glucose production. This drives FFA release from adipose tissues and causes deposition in pancreatic cells. This leads to hyperglycaemia and dyslipidaemia. The elevation in peripheral FFA exacerbates insulin resistance through inhibition of insulin stimulated glucose uptake in muscle tissue (Boden, 1999). Toll like receptor (TLR) activation by FFA causes down regulation of GLUT-4, the insulin-regulated glucose transporter in adipose tissues and striated muscle, leading to insulin resistance (Paneni et al., 2013). Skeletal muscles account for 75% of the uptake of glucose where it is utilised or stored as glycogen.

The disease progression to frank diabetes is slower in T2DM than in T1DM as patients maintain some ability to produce insulin. This prolonged onset leads to less obvious symptoms initially and a delay in diagnosis. Insulin resistance can precede clinical signs by as much as 20 years (Palicka, 2002), and patients can present with complications of the disease at diagnosis (Dall et al., 2014). As in T1DM, a combination of gene susceptibility and environmental factors act in synchrony to trigger disease. Modifiable risks include lifestyle factors and obesity. Non modifiable risk factors include family history, ethnicity and age. The risk of developing T2DM is 1.4% within the population ages 20-24 years increasing to 19.9% for those aged 75-79 years (International Diabetes Federation, 2019). There is greater heritability than that seen in T1DM with a 1 in 3 chance of disease development in those with a first degree relative with diabetes.

T2DM is usually identified as part of the "metabolic syndrome". A group of disorders that are also known risk factors for diabetes; abdominal obesity, hypertension (HTN), dyslipidaemia, a prothrombotic state and insulin resistance (Rambhade, Chakraborty, Patil, & Rambhade, 2011). Rising levels of overweight and obesity are driving the increase in diabetes rates, with most adults in western countries overweight or obese and their prevalence increasing rapidly in developing countries(Ng et al., 2014). Obesity exerts a greater risk the longer the person has been obese for, the earlier the age in which obesity develops and with the severity of obesity. Obesity is thought to contribute to diabetes through nutrient overload (high fat, protein and low exercise) and through the metabolic effects of adipose tissue.

Other lifestyle factors increasing the risk of developing T2DM include poor diet and a sedentary lifestyle. Western diets, high in fat and sugar, are associated with an increased risk of insulin resistance and ultimately of diabetes (Hu, 2011). The western food consumption pattern, high in red meat and refined carbohydrates, has been associated with a rise in inflammatory markers (Astrup & Finer, 2000; Schulze et al., 2005). This low grade pro-inflammatory state is an underlying factor in the pathogenesis of T2DM (Nowlin, Hammer, & D'Eramo Melkus, 2012).

Exercise has a substantial effect on glycaemic control, allowing for glucose regulation through a mechanism outside of insulin. During exercise, muscle utilises glucose made available by intramuscular glycogenolysis and by increased glucose uptake. Both aerobic and resistance exercise upregulate cellular GLUT-4, increasing blood glucose uptake in an insulin independent pathway. Randomised controlled trials have shown that controlling diet and exercise is as effective as pharmacological interventions for delaying the onset of T2DM with effects lasting for up to 10-23 years if interventions are maintained (Eckstein et al., 2019). A 30-50% reduced risk of T2DM has been demonstrated with lifestyle modification and pharmacological interventions for management of glucose (metformin, thiazolidinedione) and medication used to reduce obesity (orlistat) show some benefit on top of lifestyle interventions alone (Aldekhail, Logue, McLoone, & Morrison, 2015).

1.2.3.4 The diagnosis of diabetes

Diabetes is diagnosed when one, in symptomatic patients, or more of the following criteria are met - fasting plasma glucose greater than or equal to 7mmol/l (126mg/dl), a plasma glucose of 11.1 mmol/l (200mg/dl) taken randomly or two hours after an oral glucose tolerance test OGTT of 75g of oral glucose or a HbA1c of greater or equal to 48 mmol/mol (6.5%). Impaired glucose tolerance is determined if a person has both a fasting plasma glucose of less than 7 mmol/l (126mg/dl) and a plasma glucose of between 7.8 and 11 mmol/l two hours after an OGTT. Impaired fasting glucose is diagnosed if fasting glucose is between 6.1-6.9 mmol/l and if measured after a OGTT glucose is less than 7.8 mmol/l (WHO, 2020).

T1DM diabetes should be diagnosed prior to a hospital admission but around a quarter of first diagnosis globally are made when patients attend services in diabetic ketoacidosis (DKA) (International Diabetes Federation, 2019). DKA is associated with an increased risk of morbidity and mortality and can be a traumatic experience for a child and family. As discussed above, due to the slower disease process in T2DM, patients can present with complications of the disease at diagnosis(Dall et al., 2014), again associated with an increased risk of morbidity and mortality.

1.2.3.5 The management of diabetes

Treatment for T1DM and T2DM involves management of glucose levels, reducing cardiovascular mortality and monitoring and managing complications. Adequate multifactorial intervention reduces the risk of complications and ultimately premature mortality. The NICE recommends a target HbA1c of less than 6.5% together with management to reduce the risk of complications and to treat associated weight gain. Management of plasma glucose levels along with close monitoring and treatment of other cardiovascular (CV) risk factors such as hyperlipidaemia and HTN are essential for complication reduction. Physical activity and a healthy diet are a requisite part of risk reduction for complications and mortality.

In T1DM insulin is the main stay of treatment as insulin deficiency is absolute. Regular monitoring for signs of complications such as annual foot checks and retinopathy screening, education on disease management and patient and family support are also required. In T2DM the management follows a stepwise approach with lifestyle Interventions at the first step. The NICE guidelines recommend an individualised approach to diabetes management, tailored to the needs of the person so to avoid unnecessary polypharmacy and the risks of hypoglycaemia (NICE, 2015). A healthy diet, regular exercise, smoking cessation, and reduction of body weight to within a healthy range reduce the risk of further hyperglycaemia, development of complications and CV risk. Diet and exercise have been shown to be as effective as first line treatment for T2DM and are the first step for management in NICE guidelines. The oral medication metformin is the next step if diet and lifestyle change are not effective in managing hyperglycaemia. Patients then progress along the ladder of oral glucose control methods until HbA1c targets are met. HbA1c targets vary dependent on the patient and management used. For persons on medication not associated with hypoglycaemia a level of 6.5% is the target, for medication associated with hypoglycaemia the target is 7.0% (NICE, 2015) but this can be modified if persons are frail or have other contraindications. The use of HbA1c can also be compromised in patients with abnormal haemoglobin type or disturbed erythrocyte turnover. If patients have symptomatic

hyperglycaemia or HbA1c cannot be maintained under 7.5% on oral medication, or contradictions to oral medication are present, insulin therapy is initiated (NICE, 2015).

1.3 The complications of diabetes

When hyperglycaemia is not controlled, complications of diabetes are inevitable. The financial and human cost of this progression is extensive. Eighty percent of the NHS spend on diabetes is for complications, an estimated 7.7 billion in 2010/11 (N. Hex, Bartlett, Wright, Taylor, & Varley, 2012b). Cardiovascular disease (CVD) accounts for the greatest expenditure in people with diabetes (N. Hex et al., 2012b). The economic burden extends beyond healthcare costs with indirect costs from reduced productivity in the working population and requirements for social care contributing heavily to the cost burden in the UK and worldwide (ADA, 2018; N. Hex et al., 2012b).

Diabetes complications can either be acute or chronic. Acute complications, such as DKA and hypoglycaemia, occur more readily in T1DM. They can also occur in T2DM after the initiation of medications such as insulin and sulfonylureas (Zammitt & Frier, 2005). Acute complications can lead to permanent neurological sequalae and death (Cameron et al., 2014). Although less likely to occur in T2DM, hyperglycaemia, resulting in Hyperosmolar Hyperglycaemic State (HHS) has a much greater risk of death than DKA with a mortality rate of between 15-20% (JBDS, 2012). This is likely due to the age and frailty of the population developing HHS (Pasquel & Umpierrez, 2014). Hypoglycaemia can also result in lasting neurological sequalae or mortality with the number and severity of hypoglycaemic events directly associated with mortality (Cryer, 2012).

Chronic diabetes complications develop secondary to the effect of a hyperglycaemic state on small (microvascular) or large vessels (macrovascular) leading to systemic damage. This damage occurs in a state where there is a loss of glucose control, in obesity, with lipid dysregulation, in HTN and with genetic susceptibility (Paneni et al., 2013). In this environment protein modifications, autophagy, redox imbalances, inflammation and abnormal gene regulation occur

(Forbes & Cooper, 2013). In those people that develop chronic complications the risk of mortality associated with diabetes increases substantially. In a meta-analysis of complication event rates in clinical trials involving at least 1000 patients with diabetes, patients with the presence of proteinuria and CVD had a marked increase in all-cause mortality (Preiss, Sattar, & McMurray, 2011). A history of CVD was associated with a 3 fold increased risk in all cause death and 5 fold risk of mortality secondary to CVD. There is some evidence that the rate of chronic complications and associated mortality are declining in developed countries (Wendy A. Davis, Gregg, & Davis, 2020; International Diabetes Federation, 2019). With the increasing prevalence of diabetes, complications still present a massive burden on the healthcare system (N Hex, Bartlett, Wright, Taylor, & Varley, 2012a).

1.3.1 Chronic complications

Tissue damage secondary to hyperglycaemia is often indirect, resulting from damage to blood vessels and a disturbance in blood flow. A number of abnormal biochemical changes within complication prone cells in the hyperglycaemic state, independent to angiopathy, result in cellular damage (Forbes & Cooper, 2013). The speed at which normoglycaemia is established is important with evidence suggesting that once complications develop interventions are less effective (Paneni et al., 2013). Hyperglycaemic metabolic stress has been shown to cause long term damage to tissues even if normoglycaemia is established later in the disease. This has been termed metabolic memory (hyperglycaemic memory) and is thought to be due to a persistence of hyperglycaemic stress despite normalisation of glucose, driven by epigenetic modification of gene expression profiles (Lee, An, & Park, 2016). Large prospective trials have demonstrated the long-term reduction of micro and macrovascular complication rates if tight glycaemic control is established in the initial stages of diabetes. This was first identified when trials looking at intensive glycaemic control at the diagnosis of diabetes showed a significant decrease in the rate of chronic complications in T1DM (Nathan, 2014) and T2DM (Gaede et al., 2003; King, Peacock, & Donnelly, 1999) in patients within the intensive control arm of the studies. The Diabetes Control and Complications Trial demonstrated a 58% risk reduction in developing CVD through

intensive glycaemic control around diagnosis in T1DM when compared to a group who had received conventional treatment. This benefit was maintained over the 18 year follow up period, despite the glycaemic control in both arms becoming similar after the initial study ended (Nathan, 2014). Optimisation of glucose levels through the course of the disease along with management of other risk factors for complications does improve outcomes of complications and remains the cornerstone of management of complications (Ceriello, Ihnat, & Thorpe, 2009).

Complications are described as macrovascular, causing peripheral vascular disease (PVD), CVD, cerebrovascular accident (CVA) or microvascular, resulting in neuropathy, nephropathy and retinopathy (Forbes & Cooper, 2013).

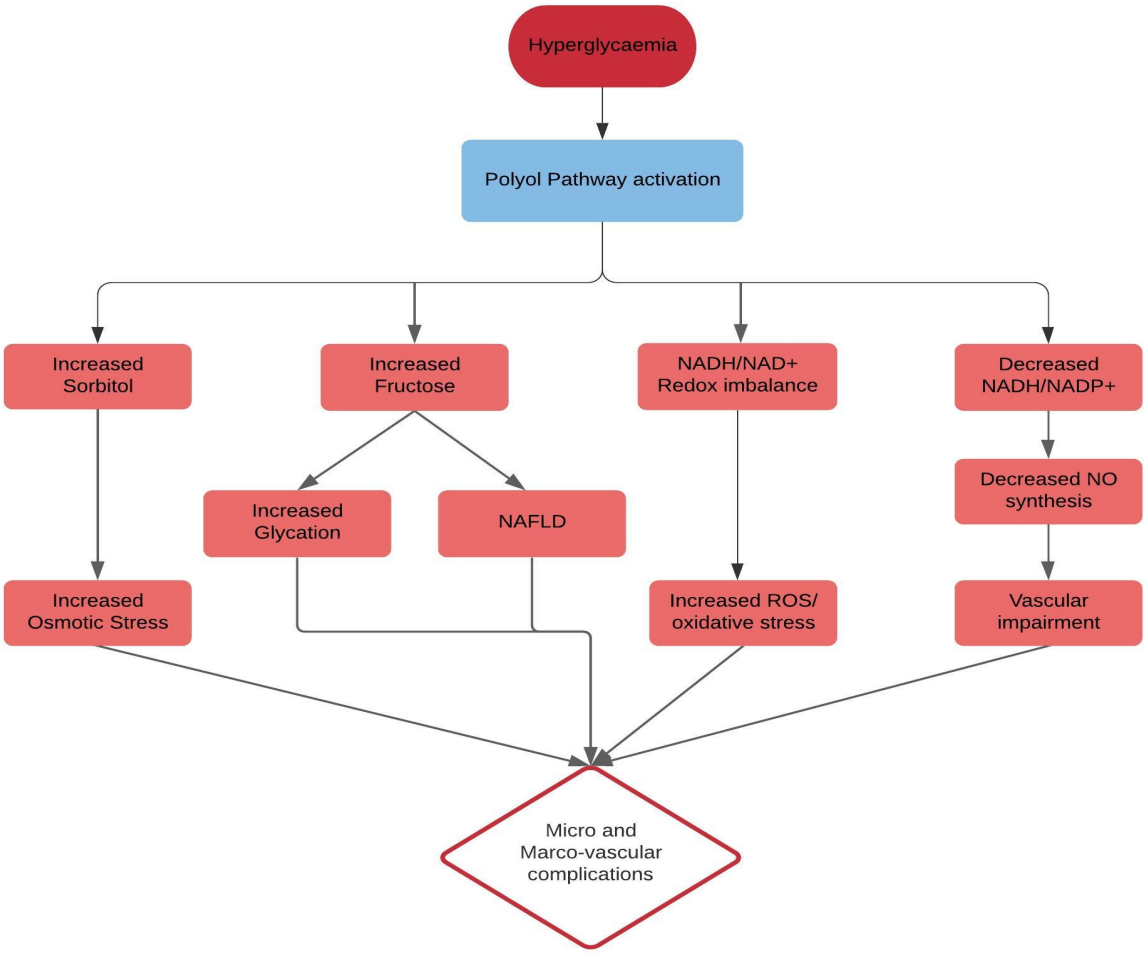
1.3.2 The pathogenesis of complications

Complications occur due to an interplay of metabolic, haemodynamic and genetic factors, resulting in complex mechanisms of damage. In complication prone tissues, dyslipidaemia and a hyperglycaemic state cause endothelial damage and inflammation through several mechanisms including changes in cell energy production and utilisation, dysregulation of nitric oxide (NO) homeostasis, formation of Advanced Glycation End Products (AGEs) and oxidative stress (Forbes & Cooper, 2013). Endothelial and smooth muscle cell dysfunction in vessels results in alteration in vascular homeostasis, leading to a prothrombotic and pro inflammatory state.

In a hyperglycaemic state complication prone cells lose the ability to modulate the appropriate transport of glucose and excessive accumulation can occur leading to abnormalities in energy production and utilisation and a change from aerobic to anaerobic production on ATP (Figure 1.2). An excess of glucose causes a downregulation of glucose transport into the cell, for preservation of the cell or through signalling function deterioration ultimately, giving a picture of perceived glucose deficiency. FFAs and amino acids (AA) are then utilised for energy production. Abnormalities in the delivery of glucose and the changed ratio of cell specific fuel sources lead to

changes in respiratory chain function, in which, potential energy is generated as ATP in the cell; specifically in the mitochondria. Electrons are passed from donors to acceptors at higher redox potential through protein complexes generating a potential difference across the mitochondrial membrane. In the hyperglycaemic state damage to the mitochondrial membrane and uncoupling of the respiratory chain occurs, liberating heat instead of energy. The changes are seen in complication prone tissues and a loss of ATP production culminates in cell death (Fowler, 2008).

Figure 1.2 Pathophysiological effects of the polyol pathway activated by persistent hyperglycaemia



Adapted from (Yan, 2018); NADH: nicotinamide adenine dinucleotide + hydrogen;. NADP: nicotinamide adenine dinucleotide phosphate; NAFLD: non-alcoholic fatty liver disease; ROS: Reactive oxygen species; NO: Nitric Oxide.

Hyperglycaemia has other deleterious effects on cell metabolism. Changes and increased activity are seen in the pentose pathway within complication prone tissues. The pentose pathway is involved in the breakdown of glucose to its by products, producing oxidised nicotinamide adenine dinucleotide phosphate (NADP+) from reduced nicotinamide adenine dinucleotide phosphate (NADPH). NADPH is key to cellular reduction-oxidation (redox) homeostasis in healthy tissues (Forbes & Cooper, 2013; Ge et al., 2020). This causes changes in protein glycosylation with the resulting sugar residues competing with phosphate groups, ultimately altering gene expression. In a hyperglycaemic environment, glucose is converted to sorbitol. Elevations in sorbitol provide the mitochondria with excess substrate to produce NADH which triggers an inflammatory response. The increase in intracellular sorbitol volume also elevates osmotic stress. This increase in osmotic stress can damage proteins and cellular components (Hao et al., 2015). The glucose / sorbitol conversion process is facilitated by aldose reductase (AR), involved in the detoxification of aldehydes to inert alcohols. In hyperglycaemia AR consumes the available NADPH inhibiting it's direct antioxidant capacity (Kirsch & De Groot, 2001) and leads to a reduced synthesis of nitic oxide (NO), reduced glutathione, taurine and myo-inositol. These changes to the phosphate pathway have been linked to microaneurysm formation, thickening of vascular basement membranes and loss of pericytes (Fowler, 2008). Overnutrition causes an increase in FFA release from adipose tissue, which up-regulates a key component of the pentose pathway, glucose-6-phosphate dehydrogenase (G6PD) expression. The elevation in G6PD worsens inflammation and drives the pentose pathway (Ge et al., 2020).

The inflammatory state associated with chronic obesity is a major cause of insulin resistance. Insulin resistance plays a key role in the progression and induction of complications in T2DM and is being increasingly noted in T1DM (Priya & Kalra, 2018). It is most commonly seen in the insulin responsive tissues the liver, skeletal muscle (SM) and adipose tissue and sites of complications such as within podocytes in the kidney. The perceived hypoglycaemic state in the liver mobilises FFA from adipose tissue and upregulates gluconeogenesis and glycolysis, further increasing the hyperglycaemic state. The accumulation of FFAs and the high glucose environment cause modulation of glucose uptake into cells at the sites of complication and FFAs reduce insulin

mediated glucose uptake in SM as discussed above. In obesity the insulin resistance is driven by adipose tissue macrophages (ATMs) (Catrysse & van Loo, 2018). They engulf dead adipocytes and secrete pro and anti-inflammatory cytokines also known as adipokines (Mancuso, 2016). In obesity there is an increase in number and function of ATMs with a shift towards the production of pro-inflammatory cytokines. The pro-inflammatory ATMs produce a greater volume of ATP and NADPH that drive the inflammatory response. The cytokines released, interleukin 1β (IL-1β) and tumour necrosis factor-α (TNF-α), alter the insulin receptor signalling pathway, contributing to systemic insulin resistance (Ge et al., 2020). Furthermore, pro-inflammatory cytokines induce lipolysis and the release of FFA from adipose tissue. The elevated levels of FFAs in the liver upregulate pyruvate carboxylase and hepatic acetyl CoA activity promoting gluconeogenesis along with increasing production of ROS in the liver causing insulin resistance and ultimately non-alcoholic steatohepatitis (NASH). As discussed above, in the pancreas, elevated circulating FFA levels advance beta-cell dysfunction (Ge et al., 2020). FFAs cause tissue inflammation through activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) which induces the production of inflammatory cytokines. FFAs also activate toll like receptors, causing down regulation of GLUT-4 and ultimately insulin resistance. Oxidation of stored FFA within cells generates ROS and leads to a cascade of pathways discussed below culminating in vascular inflammation.

Along with nutrient overload, obesity is associated with a lack of physical activity and an abnormal nutrient balance (Romieu et al., 2017). There is debate around the effect dietary fat has on the development of insulin resistance and diabetes (Rice Bradley, 2018) but studies have demonstrated that a high fat diet, increased fat content and calorie intake, can induce neuropathy in murine and human models due to oxidative stress (Dandona et al., 2001; Obrosova et al., 2007; Ozay et al., 2014). There is evidence that diets high in monounsaturated fats and polyunsaturated fats improve cardiovascular outcomes and endothelial dysfunction (de Mello et al., 2011; Shapiro, Theilla, Attal-Singer, & Singer, 2011). Calorie restricted diets have also been shown to delay cardiovascular outcomes (Hammer et al., 2008; Soare, Weiss, & Pozzilli, 2014). Exercise has been shown to reduce the formation of AGEs, insulin and cytokines which reduce

the risk of complication formation and propagation. In PVD exercise programmes form a cornerstone of management and have been shown to correct metabolic abnormalities through changing the oxidative capacity of SM, the distribution of blood flow and increasing the utilization of oxygen in tissues(Tan, 2000).

Dyslipidaemia, classified of high triglycerides and low-density lipoproteins (LDL) and low high-density lipoprotein HDL, is commonly seen in people with diabetes. The picture of high triglycerides and low HDL is identified early in T2DM and presents later in T1DM. In dyslipidaemia, cells FFA uptake increases either through passive diffusion or protein mediated pathways. Changes in the expression of these protein mediated pathways have been demonstrated in complication prone tissues (Forbes & Cooper, 2013). Dyslipidaemia plays a central role in the development of neuropathy and can occur early in the disease course of T2DM, with neuropathy present at the time of diabetes diagnosis in 10-20% of cases (Charles et al., 2011).

A number of haemodynamic changes are seen in diabetes and are associated with the proliferation of complications. HTN is associated with accelerated marco and microvascular compromise (UK Prospective Diabetes Study Group, 1998). The effects of HTN and hyperglycaemia are cumulative (Yamazaki, Hitomi, & Nishiyama, 2018). The Renin-Angiotensin-Aldosterone system (RAAS), a key component of haemodynamic control, is disrupted at many points in diabetes. There is overexpression of angiotensinogen and renin, driven by superoxide, that causes tubular necrosis of the kidney. Angiotensin II is elevated by the diabetes milieu and has a number of effects including increased renal albumin permeability. This is secondary to cytokine mediated damage of podocyte structure and function, producing fibrinolytic cytokines and causing accumulation of extracellular matrix.

Protein breakdown to their constituent amino acids occurs via autophagy. This process occurs when proteins are damaged or for fuel in low glucose environments and is tightly regulated to

maintain cellular structure and function. As insulin inhibits autophagy, in complication prone tissues, fluctuations of insulin can lead to a build-up of dysfunctional and damaged proteins. As discussed above there are a number of modifications to protein function and turnover involved in the development of diabetes and its complications. Protein synthesis and function is changed in a hyperglycaemic environment through genetic mutations and integration of posttranslational modifications leading to disruption of or incorrect folding of proteins. Phosphorylation, glycosylation and advanced glycation of amino acid chains causes Incorrect folding of proteins. Glycosylation is the addiction of glycans onto organic molecules, N-linked glycosylation occurs in the endoplasmic reticulum (ER) and o-linked in the golgi apparatus. N-linked glycosylation is disrupted in diabetes leading to an accumulation of misfolded proteins and a disruption of protein trafficking, a process termed ER stress. ER stress protective pathways are overwhelmed in diabetes by AGEs and this will ultimately initiate inflammatory and proapoptotic pathways within the cell. This process has been identified in the nephron, retina and in blood vessels. It is also seen in cardiomyocytes causing apoptosis and atherosclerosis. O-linked glycosylation is addition of galactosamine and is important for production and function of extracellular matrix proteins such as collagen. O-linked glycosylation occurs in excess in complication prone tissues in diabetes. It is especially prevalent in cardiomyocytes causing impaired calcium cycling, cardiac hypertrophy and inhibition of protein phosphorylation. Disruption to o-linked glycosylation also leads to impaired angiogenesis and damage to renal cells.

Advanced glycation is the non-enzymatic addition of sugar moieties to free and protein amino acids, producing AGEs. This is one of the most frequent processes of protein change identified in diabetes and a common driver of complications. A hyperglycaemic environment and oxidative stress accelerate the formation of AGEs leading to heavier modification of senescent proteins and abnormal glycation of functioning proteins. AGE formation leads to the release of ROS, cross links matrix proteins leading to stiffing of elastic structures and alters cell adhesion and protein interactions. AGEs have been associated specifically with pericyte loss and microaneurysms formation.(Fowler, 2008). AGEs also react with cellular receptors including receptor for advanced glycation end products (RAGE). Activation of RAGE in diabetes leads to extracellular matrix

protein fibrosis, production of chemokines, profibrotic cytokines and growth factors. Upregulation of RAGE is associated with CV events and all-cause mortality although the relationship between RAGE and complications is not straightforward with RAGE expression found to be low in early disease. AGE/RAGE modulation is upstream of a number of pathological processes seen in diabetes, ROS generation, immune system activation and cytokine upregulation and has a role in glycaemic control. RAGE activation leads to dysregulation of enzymes of vascular homeostasis through glycosylation. This reduces eNOS function and causes upregulation of inflammatory cytokines and pro inflammatory genes. The most commonly seen AGE in diabetes is HbA1c and has been demonstrated as the most useful prognostic indicator for CVD risk in T1DM and T2DM (Nathan, 2014; UKPDS, 1998). AGEs cause DNA and histone modification and are thought to be a key driver of metabolic memory(Lee et al., 2016).

Abnormal phosphorylation leads to activation of a family of intracellular secondary messengers, Protein Kinase C (PKC). It occurs in a hyperglycaemic state due to AGEs and angiotensin II. An overexpression of PKC has been associated with changes to blood flow (Freeley, Kelleher, & Long, 2011). This is secondary to changes in enzymatic activity, excessive apoptosis, basement membrane thickening, increased vascular permeability, extracellular matrix expansion, abnormal angiogenesis, inflammation and cell growth along with ROS generation. PKC decreases eNOS activity reducing the amount of NOS and NO production. It also increases production of Endothelin-1, a peptin, that initiates platelet activation and vasoconstriction. PKC activation causes upregulation of cox-2 increasing thromboxane-A2 and a reduction in prostaglandins. This induces a pro thrombotic state. Unsurprisingly this plays a central role in developing retinopathy, cardiac dysfunction, nephropathy and neuropathy. Another family of PK, mitogen-activated protein kinase (MAPK), are also abnormally activated in diabetes and initiate a cascade on intracellular events result in abnormalities in cell differentiation and apoptosis in complication prone tissues (Barros, da Silva Santos, & da Silva Reis, 2019).

In a hyperglycaemia state the pathways discussed above ultimately converge to elevate the volume of ROS and oxidative stress. Mitochondrial abnormalities and abnormalities in the polypol pathway result in elevation of hydrogen peroxide production in place of ATP. In healthy tissues the effect of ROS are mitigated by antioxidants but antioxidant function is also impaired in diabetes. NADP+, produced in the polypol pathway as discussed above, produces large volumes of superoxide in neutrophils in homeostasis to aid with phagocytosis. Superoxide acts as secondary messenger in non-phagocytic cells. However, at a high level it is damaging to cellular structure and function. Superoxide production is activated by angiotensin II, AGEs, glucose and insulin therefore is upregulated in insulin resistance and diabetes. ROS further trigger cellular mechanisms producing AGEs, PKC activation and NF-kB mediated vascular inflammation. ROS accumulate in mitochondria inducing AGE synthesis and eventually mitochondrial apoptosis. ROS induced inflammation has been implicated in atherosclerosis as it plays a role in generating foam cells(Nowak, Deng, Ruan, & Xu, 2017). Endothelial dysfunction causes an imbalance between NO production and ROS accumulation. NO, a free radical produced by numerous cell populations, has a role in cellular signalling, vascular dilation and is vaso-protective. NO is produced by NO synthase from NADPH, l-arginine and oxygen in neuronal and endothelial tissues and in inducible forms. Accumulation of free radicals in vascular endothelium leads to an injurious biochemical pathway resulting in inflammation and uncoupling of NO synthase which increases the generation of ROS. The evidence surrounding the role of NO itself in diabetes complications is mixed. NO generation is upregulated early in the disease process of neuropathy. Blockade of NO at this stage in animal models has been shown to improve nerve conduction (Zochodne & Levy, 2005). However, NO generation is downregulated in complication prone tissues in late disease secondary to glucose and AGE driven modification/inhibition of NO synthase and protective effects of NO is lost. Increasing oxidative stress inhibits NO function through the production of the pro oxidant peroxynitrite (Pall, 2013). Peroxynitrite inactivates NO and the activity of antioxidant enzymes through substrate nitration, allowing further accumulation of free radicals. Lipid dysregulation is also associated with reduction in NO production through the stimulation of asymmetric dimethylarginine (ADMA), a natural inhibitor of NO synthase. ADMAs are renally secreted and their circulating volume increases as CKD progresses (Lajer et al., 2008).

As described above, an end product of a number of the metabolic pathways activated in diabetes are inflammatory mediators. Chronic inflammatory pathways are common pathogenetic mediators in the course of both T1DM and T2DM and in diabetes complications (Tsalamandris et al., 2019). Levels of inflammatory markers, such as c-reactive Protein (CRP), are predictive for the presence and extent of CV risk in diabetes (Mugabo, Li, & Renier, 2010). In complication prone tissues, dyslipidaemia, HTN and hyperglycaemia cause endothelial damage and activation leading to inflammation through the pathways discussed above, including dysregulation of NO production, formation of AGEs, oxidative stress and NF-κB activation. NF-κB is a transcription factor and modulator of diabetic complications. It is central to transcription of angiotensinogen, cytokines and adhesion molecule and is important in modulating apoptosis. Translocation of NF-κB into the nucleus occurs in the hyperglycaemic milieu, inducing the transcription of proinflammatory molecules. Adhesion molecules lead to recruitment and extravasation of leucocytes into tissues. This is of particular importance in retinopathy and neuropathy. Reducing the volume of adhesion molecules in mice models has been shown to reduce development of retinopathy, neuropathy and atherosclerosis. Higher levels of circulating adhesion molecules have been demonstrated in patients with neuropathy (Doupis et al., 2009) and smooth muscle cell proliferation occurs in the presence of cytokines from monocytes. Along with attracting immune cells, chemotactic expression itself alters podocyte structure contributing to albuminuria and the change in cytoskeletal arrangement leads to renal hypertrophy and nephropathy. Phagocytic cells are chemotactic to other leucocytes such as T cells further increasing cytokine production.

High levels of pro-inflammatory cytokines have been shown in complication prone tissues. In neuropathy, interleukin-1 (IL-1) has been shown to contribute to nerve damage and to miscommunication to and between axons and the myelin sheath. IL6 and TNF-a are produced by white adipose tissue and raised in obesity and diabetes. In abnormal concentrations they affect glial and neuronal cell behaviour, increasing VEGF expression, contributing to retinopathy and neuropathy. TNF-a also stimulates CRP which reduces activity of eNOS and increases production

of E-1 and adhesion molecules. Cox2 another inflammatory mediator increases angiogenesis and neuropathic pain through prostaglandins and fibrosis.

Growth factors are also upregulated in inflammation. Insulin itself is a growth factor but its role in complications is complex. It is involved in the renal hypertrophy seen at the early stages of T2DM but in insulin resistance, hypotrophy of skeletal muscle ensues with an increase in the volume of the liver and adipose tissues (Perry et al., 2016). Insulin-like growth factors (IGF) also act on insulin receptors. A decrease in insulin and IGF function within the retina can lead to degeneration of vascular and neuronal tissue leading to ischaemia, whereas an increase, as seen in exogenous insulin administration can lead to neo-vascularisation and haemorrhage. TGF-B is another growth factor implicated in complications. Release is stimulated by hyperglycaemia, AGEs, angiotensin II, lipids and oxidative stress, stimulating tissue fibrosis, a key process in cardiac and vascular dysfunction. VEGF is a signalling protein stimulating neovascularisation. It is found in increased volumes in complication prone tissues but again it's affects are complex. It is known to be a key mediator of retinopathy but it has been found to be reno protective and it is expressed in vascular endothelium, increasing neovascularisation (Aiello & Wong, 2000).

A prothrombotic state is also present in diabetes secondary to mechanisms seen in a hyperglycaemic state and in disruption to insulin production and function. In homeostasis insulin inhibits platelet aggregation and thrombosis through enhancing fibrinolytic action and tissue factor inhibition. In insulin resistance, atherothrombosis is propagated through a reduction in the production of plasminogen activator and a cellular increase in synthesis of fibrinogen and plasminogen activator inhibitor-1. Hyperinsulinemia also increases pro-coagulant activity through thrombin generation and in a hypoinsulinemic and hyperglycaemic state there is a build-up of calcium in platelets, leading to a faster response and abnormal aggregation. Platelet function is further disrupted by increased NO generation, altered calcium regulation and free radical formation which promote aggregation and a hypercoagulable state (Fowler, 2008). Higher levels of microparticles produced from abnormal apoptosis and activation of cells promote

thrombus production at sites of inflammatory induced endothelial damage. The upregulation of glycoproteins, produced through glycosylation, further trigger thrombus formation through interaction with key coagulation factors, fibrin and von Willebrand factor (vWF).

1.3.3 Microvascular complications

Microvascular complications are those that occur secondary to damage to small blood vessels, typically causing neuropathy, nephropathy and retinopathy. Diabetes related nephropathy is the presence of proteinuria secondary to hyperglycaemic damage to endothelial, smooth muscle, mesangial, podocytes, tubular and collecting ducts as well as disordered function of inflammatory cells of kidney. Damage to the structures of the kidney leads to a decline in function which generally progresses over 10-20 years (International Diabetes Federation, 2019). Forty percent of the diabetes population within the UK will develop some level CKD during their lifetime (Couser, Remuzzi, Mendis, & Tonelli, 2011) and diabetes is the leading cause of end stage renal disease (ESRD) in the UK. People with diabetes are at a 10 times greater risk of requiring dialysis compared to the general population (International Diabetes Federation, 2019). ESRD can develop secondary to HTN, polyneuropathic bladder dysfunction, urinary tract infections or macrovascular angiopathy and the natural history depends on the type of diabetes. Overt nephropathy may be present at diagnosis of T2DM but typically presents later in T1DM. In T1DM once macroalbuminuria develops, 50% of patients will develop ESRD by 10 years, whereas only 20% will progress to ESRD in T2DM (Lim, 2014). The presence of nephropathy alone increases the risk of macrovascular complications such as stroke, MI and PVD (Forbes & Cooper, 2013).

Retinopathy is associated with retinal vascular permeability, capillary microaneurysms and degeneration and retinal neovascularization. Even with good glycaemic control almost all people with T1DM and T2DM will have developed retinal lesions at 20 years (Forbes & Cooper, 2013) and, as with other complications, are time dependant. The prevalence of diabetic retinopathy in the T1DM and T2DM populations in the UK is around 54.6% and 30.0% respectively (Mathur et al., 2017; R. L. Thomas et al., 2015). Outcomes such as blindness are modifiable with early

detection and treatment leading to the development of national screening programmes (Scanlon, 2017; R. L. Thomas et al., 2015). Those with T1DM are at a higher risk of developing proliferative disease and sight loss compared to those with T2DM (Forbes & Cooper, 2013).

Neuropathy will be discussed in greater detail in the context of diabetic foot disease below. Peripheral neuropathy is the most common neuropathy seen in diabetes, but neuropathies affect a number of systems including the central nervous system, somatic and autonomic nervous systems (Forbes & Cooper, 2013). Orthostatic hypotension occurs secondary to autonomic failure due to impaired baroreceptor function and damaged vasoconstrictor fibres. This results in an inability to adjust vascular tone and heart rate in response to stimulus leading to reduced cerebral blood flow (Eguchi et al., 2006). Orthostatic hypotension is associated with increased mortality and can be difficult to manage as many of the treatments for hypotension are not effective (Metzler et al., 2013). Neuropathies can affect the gastrointestinal (GI) tract, resulting in gastroparesis, nausea and diarrhoea (Forbes & Cooper, 2013). Along with organ system dysfunction, small fibre neuropathies affect wound healing, can cause erectile dysfunction and are associated with CVD through mechanisms such as cardiac autonomic neuropathy (CAD) (Callaghan, Cheng, Stables, Smith, & Feldman, 2012). CAD is associated with a five-fold increased risk of cardiovascular mortality alone (Serhiyenko & Serhiyenko, 2018) and with an increased morbidly and mortality after cardiac events (Callaghan, 2012).

1.3.4 Macrovascular complications

Macrovascular complications occur as the sequalae of premature atherosclerosis secondary to chronic inflammation and endothelial injury (Fowler, 2008). The complications are often classified as CVD despite a mix of micro and macrovascular causes contributing to CVD in the population with diabetes. For example, myocardial dysfunction and cardiomyopathy are often found independently to atherosclerotic disease (Leon & Maddox, 2015). There is a clear correlation between poor glycaemic control, CVD and mortality. Diabetes is a risk multiplier in macrovascular disease with an increased risk of atherosclerosis and CVD along with an increased

risk of poor outcomes from the disease and of complications post intervention (Forbes & Cooper, 2013).

Macrovascular complications occur along a continuum and progresses to vascular disease as hyperglycaemia continues, eventually resulting in atherothrombosis (Paneni et al., 2013). As discussed, the oxidative stress and chronic inflammation associated with diabetes alter arterial structure and function leading to a thrombogenic and pro inflammatory state (Forbes & Cooper, 2013). This is propagated by a failure of vascular repair secondary to a reduction in the function of endothelial progenitor cells (Tepper Oren et al., 2002). Damage to or activation of the endothelium through inflammation triggers a cascade, culminating in formation of an atherosclerotic plaque. Oxidised LDL particles accumulate in endothelial walls secondary to inflammation and endothelial injury. Angiotensin II promotes the oxidisation of LDL (Kita et al., 2001). There is often structural lipoprotein abnormalities seen in diabetes with a predominance of dense, small LDL particles instead of normal large LDL particles (Dokken, 2008) which is more easily oxidised and atherogenic.

Oxidised LDL attracts monocytes, which infiltrate into the vessel wall and differentiate into macrophages. These macrophages take up the oxidised lipids, forming foam cells and when accumulated in the intimal layer of the vessel wall, a fatty streak (Crowther, 2005). Fatty streaks most often occur at bifurcations in vessels and at other sites of turbulent flow. Foam cells encourage macrophage proliferation, realising inflammatory markers and attracting t-lymphocytes. Once in the subendothelial space, T-lymphocytes stimulate collagen production and matrix deposition and induce aberrant smooth muscle proliferation. Cell necrosis occurs and the process results in formation of a lipid-rich atherosclerotic plaque with a fibrous cap. The plaque may form progressive occlusion of vessels or rupture, which leads to infarction and embolus (Rader, 2007). This is along with a hypercoagulable state secondary to increased platelet adhesion and function, as described above. Impaired fibrinolysis in diabetes increases risk of vascular occlusion and CV events (Fowler, 2008).

The relative risk of CVD is between 1.6 and 2.6 compared to the general population, with CVD, affecting 32% of those with diabetes. CVD is categorised into different disorders dependant on the organ system affected and the chronicity of the disease (Dormandy, Heeck, & Vig, 1999). In diabetes the most common disorder seen is CHD with a prevalence of 21% in UK population with diabetes. Other disorders commonly seen include MI, seen in 10% of the population and cerebrovascular disease in 7.6%. The prevalence of PVD is high and this will be discussed in greater detail later in the chapter (Einarson, Acs, Ludwig, & Panton, 2018). Another presentation of CVD is diabetic cardiomyopathy, causing diastolic dysfunction of the heart which ultimately progresses to diastolic heart failure if untreated.

A predictor of CVD risk is HbA1c, along with postprandial hyperglycemia (Ceriello, 2009; Paneni et al., 2013). Within the UK Prospective Diabetes Study (UKPDS) a 12% increased risk of developing heart failure was associated with every 1% increase in HbA1c (UK Prospective Diabetes Study Group, 1998). Within Europe the majority of patients diagnosed with CVD will have some evidence of insulin resistance or diabetes. In the large Euro Heart Survey performed over 25 countries in 110 medical centers investigating 4961 subjects with coronary artery disease (CAD), defined as atherosclerosis within the coronary vessels, and no known diabetes, a majority of subjects were found to have impaired fasting glucose (5%), glucose tolerance (32%) or diabetes (18%) (Bartnik et al., 2004). Not only are CV disorders prevalent in the diabetes population, the risk of developing the disorders is greatly increased in those with hyperglycaemia (106% increased risk of all CV disorders, CVD 127% and stroke 56% compared to the general population) (Sarwar et al., 2010) and with the length of disease (Wannamethee et al., 2011). Although the risk of CVD is increased, it is less clear if the risk of cardiovascular outcomes is greater than in the general population (Beckman, Paneni, Cosentino, & Creager, 2013). In a large metanalysis comprising of 45,108 persons, those with diabetes alone had a 43% lower risk of developing CV events than patients without diabetes but with previous myocardial infarction (MI) (Bulugahapitiya, Siyambalapitiya, Sithole, & Idris, 2009). However, since the analysed studies were produced, the threshold for diabetes diagnosis has changed and the effect seen may have been due to inclusion of a lower risk population. Along with a greater risk of CVD, there is also

greater mortality after MI and poorer outcomes from interventions such as a higher rate of stent thrombosis following revascularisation post MI (Beckman et al., 2013). As for microvascular complications there are differences in disease profiles between T1DM and T2DM. In T1DM, CVD is unlikely to develop unless there is an element of nephropathy. In T2DM this is not the case, perhaps due to the presence of other independent risk factors for CVD such as dyslipidaemia and obesity (Beckman et al., 2013).

The presence of diabetes also infers an increased risk of developing cerebrovascular disease. In a large international case-control study across 32 countries, the diagnosis of diabetes increased risk of stroke when compared to the background population by 35% and was found to be responsible for 5% of the population attributable risk of stroke (O'Donnell et al., 2016). Other population studies have demonstrated a 127% increased risk of ischemic stroke and 56% excess rate of haemorrhagic stroke in the population with diabetes (Beckman et al., 2013).

There is an abundance of evidence demonstrating the risk of CVD associated with diabetes, but the relationship is complex with a number of risk factors for CVD beyond hyperglycaemia seen within the population with diabetes. Dyslipidaemia is strongly associated with atherosclerosis, and dyslipidaemia is commonly seen in the population with diabetes especially in those with concomitant obesity (Wu & Parhofer, 2014). The risk factors for all CVD are similar and can be classified as modifiable, non-modifiable and existing disease (Donnelly & Powell, 2011). Existing disease beyond diabetes includes a history of CVD. Non-modifiable risk factors include increasing age, male gender, ethnicity, low socioeconomic status and family history of CVD and modifiable risk factors can be lifestyle related such as smoking history, insufficient physical exercise and poor diet or associated with metabolic syndrome; obesity, HTN, dyslipidaemia and poor glycaemic control along with CKD and rheumatoid arthritis (Beckman et al., 2013). Risk factors often occur in clusters creating a cumulative effect. In a large prospective study of CVD risk, Wilson et al, found risk increased from 4-fold with 1 risk factor to 60-fold in men in the presence of 5 risk factors (Wilson, Kannel, Silbershatz, & D'Agostino, 1999). With multiple risk factors occurring in

70% of those at risk of CVD it is important to address modifiable risks in unison (Dahlöf, 2010). This is especially true as reductions in morbidity and mortality are seen with modifiable risk factor reduction for CVD (Beckman et al., 2013).

1.3.5 The management of complications

Hyperglycaemic control is a cornerstone of diabetes management. As discussed above, tight initial control of glycaemia has a legacy effect and an increased risk of complications, such as CVD and neuropathy is seen in hyperglycaemia. A meta-analysis of the main studies examining cardiovascular outcomes and tight vs routine glycaemic control demonstrated a 17% reduced risk of MI, but no significant reduction in risk of stroke or all-cause mortality (Hemmingsen et al., 2011). Glycaemic control is achieved through different mechanisms for each type of diabetes with exogenous insulin being the main treatment for T1DM and a stepwise approach from exercise and lifestyle to insulin therapy in T2DM.

For many of the oral hypoglycaemics used in T2DM, their role in management goes beyond glucose reduction. Thiazolidinediones may be renoprotective, reducing profibrotic cytokine production and reducing activation of proximal tubular cells in animal studies (Sarafidis & Bakris, 2006) along with triglyceride and blood pressure reduction and HDL elevation. In human studies Thiazolidinediones have been shown to reduce urinary albumin excretion and are associated with lower risk for progression to ESRD necessitating dialysis in cohort studies (Chen et al., 2015; Sarafidis et al., 2010). However, this has not been replicated in randomised controlled trails (Inzucchi & Lupsa, 2021). Metformin has been shown to have beneficial effects on macrovascular complications (King et al., 1999), and especially CVD and MI risk when compared to other oral hypoglycaemics. Metformin also shows a favourable effect on retinopathy. The UKPDS study demonstrated a 27% reduction in all cause mortality and a 33% reduction in MI incidence at 5 years in overweight patients given metformin vs sulphynylureas despite equivalent glycaemic control (King et al., 1999). This finding was mirrored in the REACH study with a 24% reduction in all-cause mortality seen in those on metformin vs those who were not even following previous

MI (Roussel et al., 2010). Improvements are felt to be secondary to the reduction of dyslipidaemia and the pro-inflammatory and pro-coagulative state. Decreased carbonyl and oxidative stress and improvements in endothelial function have been demonstrated with metformin use (Grant, 2003). There has been some controversy surrounding antiglycaemic agents and cardiovascular risk following the release of a number of medications that increased CV end points. This risk was detected only on meta-analysis of clinical trial data, such as for the thiazolidinedione rosiglitazone (Panicker, Karnad, Salvi, & Kothari, 2012). Since this finding all oral antiglycaemic medications much undergo cardiovascular safety trials to exclude increased CV risk before licencing (Fei, Tsoi, & Cheung, 2019).

Although glucose control is the cornerstone of management of risk, it is not adequate alone. The beneficial effect of managing other CV risk factors is additive. Intensive control of all risk factors was demonstrated to reduce CV risk and mortality when compared with standard treatment in the Steno-2 study (Gaede et al., 2003). HTN is associated with accelerated micro and macrovascular complications (UK Prospective Diabetes Study Group, 1998) and is a propagator of diabetes related renal disease. As in the general population, hypertensive control is the cornerstone in management of CV risk. The first line treatment recommended by NICE is either an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) along with lifestyle modification. More aggressive control is recommended for people with diabetes with the target to reach a blood pressure of 135/85 mmHg (NICE, 2019). In the UKPDS study (King et al., 1999) a 44% reduction in stroke and a 32% reduction in diabetes related death was seen in the tight HTN control arm vs the standard control arm. Unlike for tight hyperglycaemia control no legacy affect with treatment has been demonstrated (Beckman et al., 2013). A number of trails have demonstrated an optimal diastolic pressure to reduce cardiovascular and microvascular outcomes to be 80 mmHg as a significant decrease in mortality is seen with intensive blood pressure control when compared with standard treatment (Ginsberg, 2011; Safar, Blacher, & Staessen, 1998; Schrier, Estacio, & Jeffers, 1996). Despite this, aggressive control of blood pressure has been associated with a significant increase in medication related adverse outcomes (Ginsberg, 2011). Consideration of initial therapy to use is important. A large meta-

analysis of 94,492 patients with HTN demonstrated that the use of a beta-blocker for first line therapy in the general population increased the risk of new onset diabetes by 22% and increased the risk of stoke by 15% compared to other agents (Bangalore, Parkar, Grossman, & Messerli, 2007). However, this has not replicated subsequent studies (Shen et al., 2013). If treatment is started after a cardiac event, ACE inhibitors have been demonstrated to reduce rates of MI, stroke and death(Ginsberg, 2011; Sleight, 2000).

As discussed above lipid dysregulation, with a profile of raised triglycerides and LDL with low HDL, is often seen in T2DM (A. M. Vincent, Hinder, Pop-Busui, & Feldman, 2009). Along with lifestyle advice, treatment with statins has been shown to reduce risk of non-fatal MI, major coronary events, stroke, revascularisation failure and all cause death in all people with diabetes apart from those with ESRD undergoing dialysis (Kamari, Bitzur, Cohen, Shaish, & Harats, 2009; Wanner et al., 2005). In a large meta-analysis looking at 18,686 patients with diabetes there was a beneficial effect on CV outcomes and all-cause mortality with the use of statins in both those with and without a history of CV disease. There was an almost linear relationship between reduction in LDL cholesterol and risk reduction (Kearney et al., 2008). There is less convincing evidence for other lipid management medication such as fenofibrate or niacin. This may be due to the secondary effects of statins. Statins have been shown to reduce the risk of developing CVD outside of their effects on cholesterol, potentially through an anti-inflammatory affect (T. M. Davis, Yeap, Davis, & Bruce, 2008). There has been some controversy recently with regards to statins increasing the risk of developing diabetes and increasing hyperglycaemia in populations at low and high-risk for developing diabetes (Crandall et al., 2017). Despite this, statins remain the first line recommendation for primary and secondary prevention of CVD as various analyses have demonstrated that the CV and mortality benefits outweigh the diabetes risk(Subedi et al., 2013). Fenofibrates have also been demonstrated to reduce the risk of amputation, however the exact mechanism is unclear (Desai et al., 2018; Rajamani et al., 2009)

A prothrombotic state is present in diabetes and is known to contribute to the development of micro and microvascular complications. Despite this, meta-analysis of the use of aspirin in the primary prevention of CV outcomes in diabetes have failed to demonstrate a benefit (De Berardis et al., 2009; Mahmoud, Gad, Elgendy, Elgendy, & Bavry, 2019). These findings have come into question following a large RCT looking at 15480 patients with diabetes. The study demonstrated that low dose aspirin reduced MI, stroke and CV mortality by 12% at 12 years. However, the beneficial effects were overshadowed by the 29% increased risk of bleeding events in the aspirin group (Bowman et al., 2018). NICE guidelines do not recommend any antiplatelet therapy for primary prevention of CV events in diabetes but does recommend their use in secondary prevention. Differing antiplatelet agents are recommended for secondary prevention dependant on the CVD present. In PVD clopidogrel is recommended for lifelong therapy in the presence of symptoms if no contraindication is present (Sagar, Naseem, & Ajjan, 2020).

1.4 The Diabetic foot

Diabetic foot disease is a spectrum of disorders caused by the confluence of both micro and macrovascular complications. It is caused by an aetiologic triad. Neuropathy, and ischaemia secondary to PVD increase the risk of skin barrier destruction, increasing the risk of infection of the foot. These changes ultimately lead to ulcer formation, infection and Charcot foot. Along with the aetiological triad, multiple contributing causative factors work in synchrony in the development of foot ulcers (Pendsey, 2010). Diabetic foot complications will affect an estimated 40-60-million people with diabetes worldwide. Approximately 15-20% of people with diabetes will develop diabetic foot disease at some point during the course of their diabetes (International Diabetes Federation, 2019; Pérez-Panero, Ruiz-Muñoz, Cuesta-Vargas, & Gónzalez-Sánchez, 2019). The population with diabetes in the western world have a 2.5% annual risk of developing a foot ulcer (K. M. Pickwell et al., 2013). Approximately 50% of people with diabetes will develop neuropathy and this is responsible for the majority of foot ulceration. Once neuropathy develops the risk of ulceration increases to 6.3% annually compared to a 0.5% annual risk for people with diabetes without neuropathy (McGill, Molyneaux, & Yue, 2005). Although it is not the most

prevalent complication of diabetes, foot problems are responsible for 25% of all diabetes related hospital admissions in the UK and USA. Globally every 20-40 dollars of diabetes care resources are spent on the diabetic foot (Lepäntalo et al., 2011). Phillips et al, (Phillips et al., 2016) estimated that 24,000 hospital admissions occur annually in the UK due to complications of the diabetic foot. Nonetheless, with appropriate diagnosis and treatment, much of the burden associated with diabetic foot disease could be avoided (Alavi et al., 2014; Neads, 2017). Investing in prevention and early intervention foot-care strategies has been deemed cost effective and avoids the burden of often extremely costly reactive interventions (National Health Service Confederation, 2016).

Along with the vast financial burden, the impact of diabetic foot disease on patients and the population is substantial. For the individual, foot disease is associated with disability, long hospital admissions and high health care costs. Advancing foot disease is associated with poor health outcomes, reduced mobility and social isolation. Health related quality of life scores are negatively correlated with disease progression and unsurprisingly an association to depression has been identified (Navarro-Flores & Cauli, 2020; Steel, Reece, & Daw, 2016). Worryingly, diminishing health related quality of life scores are associated with poor adherence to foot care behaviours, thus, increasing the risk of further complications (Saleh, Mumu, Ara, Hafez, & Ali, 2014; Steel et al., 2016) and ultimately, diabetic foot disease leads to amputation.

1.4.1 The pathogenesis of the Diabetic foot

It is generally accepted that a triad of complications contribute to produce foot disease. Neuropathy and PVD are primary issues that precede a secondary infection, however any of these complications can precede foot disease alone or present synergistically.

1.4.2 Peripheral neuropathy

Peripheral neuropathy is classified by segmental demyelination of nerves, leading to axon and nerve fibre loss (Sharma & Thomas, 1974). In the population with peripheral neuropathy the risk of ulcer development and recurrence is 66%. The risk of amputation in this population is greater than double that of the diabetes population without neuropathy at 12% compared to 5% (Galkowska, Olszewski, Wojewodzka, Rosinski, & Karnafel, 2006).

1.4.2.1 The burden of peripheral neuropathy

Reported rates of peripheral neuropathy in diabetes vary between 13-50%. The estimate is broad as the quantity and quality of epidemiological data on symptomatic neuropathy is poor. This is due to a lack of population-based studies and varied definitions of neuropathy within the literature along with diverse criteria for diagnosis (Iqbal et al., 2018). The consensus view is over 50% of people with diabetes will be affected with neuropathy of any kind within their lifetime with peripheral neuropathy being the most common form of neuropathy accounting for 75% of the burden of disease (Forbes & Cooper, 2013; Pop-Busui et al., 2017). Peripheral neuropathy can affect the somatic, motor and autonomic nervous systems. (Selvarajah, Wilkinson, Davies, Gandhi, & Tesfaye, 2011; Selvarajah et al., 2006; S. Tesfaye et al., 2016)

Peripheral neuropathy is a neuropathy of the peripheral nerves, most commonly presenting with a symmetrical distribution, primarily in the most distal nerves first, thus, affecting the feet. As discussed above, neuropathy is also involved in erectile dysfunction, CV dysfunction, gastric motility issues and wound healing although the disease process involved in its role in these disorders has not yet been clearly described (Forbes & Cooper, 2013).

1.4.2.2 The risk factors for peripheral neuropathy

The main risk factors for neuropathy are duration of diabetes (Braffett et al., 2020), hyperglycaemia, increasing height, elevated triglyceride and LDL levels, HTN, smoking history and obesity (Bartnik et al., 2004; Iqbal et al., 2018). Tight insulin control maintaining normoglycaemia has been demonstrated to reduce the risk of neuropathy by 60% in T1DM (Diabetes Control and Complications Trial Research Group et al., 1993) and this was associated with at least an 8 year legacy effect (Martin et al., 2006). The relationship between normoglycaemia and neuropathic risk protection is less straightforward in people with T2DM. There is some discordance in the literature with some trials showing a protective effect (Martin et al., 2006) and others showing no protective benefit or legacy effect despite showing benefit on the prevalence of retinopathy and nephropathy (UK Prospective Diabetes Study (UKPDS) Group, 1998).

Despite dyslipidaemia being an independent risk factor for neuropathy the relationship between diabetes related peripheral neuropathy and dyslipidaemia is still debated. Two recent metaanalysis recorded contradictory results. A meta-analysis of risk factors for peripheral neuropathy, including 12,116 participants with T2DM in 16 cross sectional studies, demonstrated no significant increase in risk associated with increasing total triglyceride or cholesterol (X. Liu, Xu, An, & Zeng, 2019). This finding was contraindicated by another large meta-analysis of 32,668 patients with both T1DM and T2DM examining lipid profile in the predication of diabetic neuropathy in 39 studies (Cai, Yang, & Zhang, 2021). As to be expected, the meta-analysis indicated that lipid changes are among the biological changes in diabetes. Higher triglyceride (Odds Ratio (OR) 1.36, 95% CI: 1.20-1.54) and LDL levels (OR 1.10, 95%CI: 1.02-1.19) were significantly associated with a higher risk of neuropathy and increasing HDL levels were significantly associated with a lower risk (OR 0.85, 95% CI: 0.75-0.96). The study also demonstrated a significant difference in lipid profile between diabetes types, which may in part explain the lack of association seen by Liu et al, when only T2DM was explored, and HDL cholesterol was not considered. These findings were reflected in large prospective studies looking at specific populations. In the SEARCH study assessing the risk of peripheral neuropathy in those

aged less than 18 years, an increase in LDL and decease in HDL was associated with an increased risk of neuropathy in T1DM but HDL alone was associated with neuropathy in T2DM (Hamman et al., 2014). In the DCCT/EDIC study of T1DM, higher triglyceride and lower HDL levels were associated with the risk of neuropathy after adjusting for age and glycaemic control. Total cholesterol, LDL and hyperlipidaemia specifically were not associated, again suggesting the lipid profile explored in the first meta-analysis may not have been adequately specific (Braffett et al., 2020). The exact mechanism by which hyperlipidaemia influences neuropathy has not been elucidated. It is postulated that it is due to dyslipidaemias contribution to insulin resistance, oxidative stress and focal demyelination as shown in murine modes (Cai et al, 2021; Xei et al, 2013).

1.4.2.3 The pathogenesis of peripheral neuropathy

The development of peripheral neuropathy is multifactorial, with damage to both the neuronal tissue and blood supply to the nerves. It is primarily driven by hyperglycaemia, initiating the metabolic cascade described above, with resultant tissue damage. Polyol flux regulated by aldose reductase in the metabolic cascade contributes to ischaemia and reperfusion causing polyol activation and severe tissue injury. This ischemia/reperfusion injury occurs commonly in endothelial tissues and nerves and is thought to play a role in formation of neuropathy (Nukada, 2014). Glycation also occurs in nerve tissues. AGEs have been identified in every part of peripheral nervous tissue in human and animal models of neuropathy. AGEs are associated with Schwann cell apoptosis and a reduction in density of myelinated nerve fibres. An inflammatory environment is triggered by high AGE and accumulation of inflammatory cells and proinflammatory mediators lead to apoptosis. Axonal cytoskeleton glycation reduces axonal transport and causes degeneration of distal fibres, as well as reducing the axons ability to regenerate. Increased AGE also cause a reduction in endothelial cell structure and function, as in other microvascular disease, as already described. As peripheral nerves lack autoregulation in their vascular supply and arteriolar supply is sparse (D. R. Smith, Kobrine, & Rizzoli, 1977) they are particularly vulnerable to ischaemia. Within the ganglion and nerve terminal, leaking of

endoneurial micro vessels causes damage to the endoneurial tissue. When examined postmortem, thickened abnormal membranes are seen in micro vessels along with pericyte cell debris and disrupted endothelial cells (Thrainsdottir et al., 2003).

There is some debate as to whether neuropathy is a microvascular disease, as it is classically described, in which damage to the nerve vasculature is the initiating step resulting in neuronal loss through hypoxia, or whether glial and neuronal damage occurs first which then leads to vascular disarray (Forbes & Cooper, 2013). Regardless of the physiological pathway, the end result is axon dysfunction with nerve oedema, endoneurial microangiopathy and demyelination (Tomic-Canic & Brem, 2004), with predominately distal and sensory nerve fibre damage. Small nerve fibres are damaged initially with eventual progression to larger fibres. This presents as an initial loss of pain and thermal sensation followed by vibration sense and progression to complete paraesthesia. However around 25% of individuals with neuropathy may develop neuropathic pain, often with associated hyperalgesia and allodynia(Abbott, Malik, van Ross, Kulkarni, & Boulton, 2011). Ultimately all motor, sensory and autonomic nerves are affected leading to loss of proprioception, pressure and vibration sense and eventually gait changes. It is often the most peripheral sites, such as the feet, which are affected first. This is thought to be due to the length of the nerve, with an association between length and risk of neuropathy giving rise to the classic stocking and glove distribution. Longer nerves have relatively small cell bodies compared to the length of axon. When damage occurs, distal axons cannot support the full length of transport of nutrients and other signals. Earlier loss of conduction velocities and of nerve terminals have been demonstrated in longer nerves (Solomon Tesfaye & Selvarajah, 2012). Sensory neuropathy causes a loss of spatial awareness, lack of awareness of abnormal stresses and a lack of protective sensation (Yamagishi & Imaizumi, 2005) increasing the risk of sustaining an unnoticed injury and ultimately tissue loss. (D. G. Armstrong & Lavery, 1998). Trauma to the foot, such as from heat, friction and pressure from poorly fitted shoes and blunt or sharp injury from debris in footwear, can occur unnoticed. Damage can progress substantially and there is often a long delay between injury and recognition as patients cannot normally perceive the signs of injury.

Peripheral myelinated motor fibres are affected in a length dependant manner, longest to shortest. The first sign of which is the loss of achilles tendon reflex (Bandyk, 2018). Loss of muscle innervation leads to atrophy of the small muscles of the foot essential for foot stabilisation, the lumbricals and interossei. There is an imbalance of fine motor control and flexion and extension abnormalities causing a change to the foot arch and an increase in extensor tendon forces and splaying of foot on weightbearing altering the biomechanics of the foot (Lepäntalo et al., 2011). A claw toe deformity often occurs with depression of metatarsal heads, hammer toe of digits and an equine ankle deformity (Bandyk, 2018). These changed create abnormal pressure points and along with autonomic and sensory dysfunction cause loss of control of balance and posture as afferent and efferent nerve pathways to the limb are affected (Uccioli et al., 1995). Glycation is also seen within the tendons of the foot, especially of the achilles. This leads to shortening which further increasing the abnormal pressure through the foot. Continuous excess pressure causes callous formation, along with atrophy of plantar fat pads which can developed into ulceration. Continuous abnormal pressure can also lead bone destruction if inflammation occurs, a condition known as Charcot neuro-osteoarthropathy, commonly known as Charcot foot (Kaynak, Birsel, Güven, & Oğüt, 2013). Abnormal gait is worsened by the concomitant sensory neuropathy as there is loss of joint position and movement proprioception (van Deursen & Simoneau, 1999). There is also loss of autonomic nerve function in the epidermis and dermis of the foot, causing impaired thermoregulation, small vessel function and anhidrosis. Anhidrosis leads to abnormally dry skin making the foot prone to fissures particularly in calloused areas, diminishing the skin barrier and allowing for the penetration of micro-organism (Bandyk, 2018). This ‘autosympathectomy’ (Vinik, Maser, Mitchell, & Freeman, 2003) combined with the poor blood flow and reduced healing seen in diabetes markedly increases the risk of ulceration and ultimately limb loss (Bandyk, 2018).

The loss of autonomic tone in small vessels of the foot leads to a decrease in nutritive flow secondary to opening of arterial-venous (AV) shunts and precapillary sphincter malfunction. Changes in blood flow to tissues are thought to be the primary causative factor in Charcot foot (Hilz, Hecht, Berghoff, Singer, & Neundoerfer, 2000). AV shunting within the foot leads to dilated

dorsal veins, increased blood flow and erythema. Increased blood flow within the bones of the foot induces bone reabsorption, reducing bone mineral density, increasing fracture risk. (Rogers et al., 2011). Interestingly, patients with PVD have been found to be relatively protected from Charcot foot as arterial flow is restricted (Rogers at al., 2011).

A severe but uncommon complication of neuropathy is Charcot foot. It has an incidence of 2% in the population with diabetes and has a high associated risk of amputation when compared to the presence of an ulcer alone, and increases the risk of amputation if present with an ulcer (M.-W. Sohn, Stuck, Pinzur, Lee, & Budiman-Mak, 2010). Charcot foot is often misdiagnosed in its early stages as it can mimic infection or injury and presentation may be delayed due to a lack of pain (NICE, 2015). As such, there is suspected underestimation of frequency of the disease (Rogers at al., 2011). Thirty six percent of patients present with trauma and 12% a foot injury in the preceding six months prior to diagnosis (Kaynak et al., 2013). Repeated trauma leads to unnoticed fractures, tissue inflammation and tendon disruption which eventually causes a convex foot with a rocker-bottom appearance (Kaynak et al., 2013). As with motor nerve dysfunction, the deformity causes abnormal pressure points. In Charcot foot this is usually present at the inferior aspect of the cuboid and medial aspect of navicular bone in the midfoot. Aseptic inflammation occurs secondary to continued weight bearing on a fracture or injury which accelerates bone loss through bone turnover promoted by inflammatory cytokines. Ongoing inflammation increases the risk of tissue breakdown and sinus tract formation to deeper planes of tissue, allowing for deep fascial infection, ulceration and an increased risk of osteomyelitis (OM). There is also impaired cellular turnover within the foot and ankle bones, further increasing fracture risk (Kaynak et al., 2013). A marked local inflammatory response is seen with minimal systemic response. This increases the risk of misdiagnosis as there is often little to no change seen on routine blood tests (M.-W. Sohn et al., 2010). If patients are properly diagnosed and immobilised the inflammatory response will resolve and this can halt bone destruction and stabilise the disease. If missed, sustained mobilisation allows for further malformation, ligament stress and fracture dislocations of the forefoot and midfoot. Not every patient with neuropathy will go on to develop a Charcot foot and it has been postulated that there is a difference in the form of

neuropathy seen in this population but this has not yet been widely accepted (Stevens, Edmonds, Foster, & Watkins, 1992).

1.4.2.4 The management of peripheral neuropathy

At present there is no management option that can target or reverse the underlying nerve damage once it occurs therefore most treatments are aimed at prevention and the slowing of disease progression. Early detection is key to allow for early intervention and as such, annual diabetes checks include examination for neuropathy as standard (Pop-Busui et al., 2017). Tight glucose control markedly reduces the risk of developing peripheral neuropathy in the T1DM population. In a number of large trials examining intensive insulin therapy, the estimated risk reduction was 60-75% at 5 years (Braffett et al., 2020; Diabetes Control and Complications Trial Research Group et al., 1993; Linn, Ortac, Laube, & Federlin, 1996). The risk reduction associated with tight glucose control is less in T2DM (5-9%) and as discussed above, patients often have neuropathy at the onset of disease (Ginsberg, 2011). This is likely due to the longer onset of disease with a prolonged period of asymptomatic hyperglycaemia and the interplay with other metabolic risk factors such as obesity and hyperlipidaemia. Interestingly the regime used for glucose control influenced the occurrence of neuropathy, with Pop-Busui et al, identifying that insulin sensitising treatments (metformin or thiazolidinediones) reduced the incidence of peripheral neuropathy development when compared with insulin providing treatments (sulfonylureas or meglitinides and insulin) (Pop-Busui et al., 2013). This was felt to be due to the concomitant effects on metabolic factors such as dyslipidaemia and chronic inflammation along with a reduced weight gain that is not seen with insulin alone. There is some evidence that control of lipids slows progression of peripheral neuropathy in animal models; at present no trials have adequately evaluated the affect in humans (Iqbal et al., 2018).

1.4.3 Peripheral vascular disease

PVD is a progressive atherosclerotic arterial occlusive disease of the lower limbs. It plays an important role in the development of the diabetic foot as any injury, such as ulceration from neuropathy, requires adequate tissue perfusion for healing. In the presence of PVD blood flow to the tissues is not adequate for the healing of short term and chronic wounds. Overall, 50% of diabetic foot ulcers are associated with neuroischaemia or ischemia (Lepäntalo et al., 2011) and an estimated 90% of patients with diabetes undergoing amputation have ischaemia.

1.4.3.1 The burden of peripheral vascular disease

PVD classically presents with intermittent claudication but can cause a spectrum of disease ranging in severity from an asymptomatic state to absent peripheral pulses, ulcer development, gangrene and ultimately amputation. Associated symptoms that can indicate the presence of PVD include thin or shiny skin, an absence of hair on the lower limb, nail thickening and brittleness, palor on elevation of the limb and dependant redness with skin that is cool to touch. One third of the population with PVD are asymptomatic and 50% of people with PVD are thought 42 to never seek medical attention. The ratio of asymptomatic patients is likely higher in those with diabetes (Norgren et al., 2007) as pain perception may be reduced by the presence of neuropathy (American Diabetes Association, 2003). The International Diabetes Federation (IDF) reports that approximately 50% of patients with diabetes and PVD are asymptomatic and a further 33% present with atypical symptoms (IDF, 2019).

As the majority of PVD in the population with diabetes is asymptotic or atypical there have been difficulties in quantifying the exact burden of disease. Estimates of the prevalence of PVD associated with diabetes in the western world range from 9.5% in those over the age of 40 years to an estimated one in three patients over the age of 50 years (Diabetes.co.uk, 2019) with some studies reporting as many as 71% of people will develop PVD at some point (Beckman et al., 2013). The presence of diabetes increases the risk of developing PVD and in those with PVD in

the general population, 20-30% have a concurrent diagnosis of diabetes. The Framingham heart study demonstrated that patients with diabetes had a 3.5% to 8.6% increased risk of developing PVD and in the Hoorn study 20.9% of patients with diabetes had ankle brachial pressure index (ABPI) of less than 0.9, compared to 7% of those with normoglycaemia. As in neuropathy, there is variation in the risk of disease between the types of diabetes. Risk is much greater in those with T1DM, Zander et al, demonstrated a 28.9% increased risk of developing PVD at 20-29 years after T1DM diagnosis, comparatively only a 4.3% increased risk was seen in those with T2DM (Zander et al., 2002).

As well as an increased risk of developing PVD, those with diabetes are at an increased risk of disease progression and have greater morbidity and mortality. In patients with asymptomatic PVD, within 5 years 75% will have stable disease, 20% will have disease progression and <5% will require major amputation (Timaran & Timaran, 2014). Over the course of the disease, diabetes is associated with a 3-4 fold increased risk of mortality along with a 4 fold increased risk of amputation compared to the general population with PVD. People with diabetes are more likely to present initially with more severe complications of PVD such as critical limb ischaemia (CLI), ulcer and gangrene, rather than the classic presentation of intermittent claudication. CLI is the end stage complication of PVD, it is disease that has progressed to cause a symptomatic reduction in blood supply. The estimated European prevalence of CLI is between 500-1000 per million population (Norgren et al., 2007). The risk of CLI is four times higher in the population with diabetes, and once CLI develops, 50% will develop CLI in the contralateral limb within 5 years (Beckman et al., 2013). Of the patients with diabetes and asymptomatic PVD, 16% will develop intermittent claudication, 3% CLI and 1.6% will require a major amputation over the following 6-year period (Naseer Ahmad, Thomas, Gill, Chan, & Torella, 2014; Timaran & Timaran, 2014). Moreover, greater than 50% of patients with CLI in the general population have diabetes (Thiruvoipati, Kielhorn, & Armstrong, 2015). In a systematic review, CLI was associated with a 15-20% 1-year amputation risk and a 15-40% 1-year mortality risk in the general population. In the diabetes population once CLI develops there was a markedly larger 30% risk of major amputation and a 20% risk of mortality at 6 months (Thiruvoipati et al., 2015). Along with amputation risk, in

the general and diabetes population the presence of PVD increases the risk of major CV events along with their associated mortality. A 10 fold increased risk of CV events and a 25% 5 year mortality from all CV causes is seen (Fowkes et al., 2008). Outcomes are also poorer following revascularisation, likely secondary to the pattern of arterial involvement which will be discussed further below.

1.4.3.2 The risk factors for peripheral vascular disease

The burden of PVD is associated with increasing age. An estimated 29% of patients aged between 50-69 years with diabetes have PVD, the same number as those aged >70 years in the population without diabetes (Fowkes et al., 2013). The risk of developing PVD in diabetes is 3.5 times higher in men and 8.6 times higher in women (Thiruvoipati et al., 2015) than in those without diabetes. This gender-based difference is due in part to the low rates of PVD in the female population without diabetes, driven by the protective effects of oestrogen, variance in smoking status and in distribution of fat (Schramm & Rochon, 2018). PVD is also associated with severity of diabetes. In the UKPDS study, each 1-point increase in HbA1c was associated with a 28% increased risk of developing PVD along with its associated morbidity and mortality. As discussed, outcomes are also worse in those with diabetes with longer hospital stays, a greater risk of complications and higher mortality seen. There too is an association with duration of diabetes. The relative risk of PVD diagnosis is 1.39 at 1-5 years following a diagnosis of diabetes, this increases to 4.5 at greater than 25 years following diagnosis. Outside of diabetes, the risk factors for PVD are the same as seen in the general population; smoking, dyslipidaemia and HTN. Smoking and dyslipidaemia, specifically hypercholesteremia, have both been shown to double the risk of developing PVD (Aboyans et al., 2006). In the UKPDS, hypertension and specifically raised systolic blood pressure (SBP) was a discreate risk factor for PVD. Each 10mmHg increase in SBP was associated with a 25% increased risk in developing PVD over the length of the study. Individual risks act synergistically to increase the risk of PVD and the effect of PVD and diabetes on amputation risk is additive. In a large retrospective study of almost 62,300 inpatients patients, patients with a documented history of PVD and diabetes had a higher documented history of amputation at 47%,

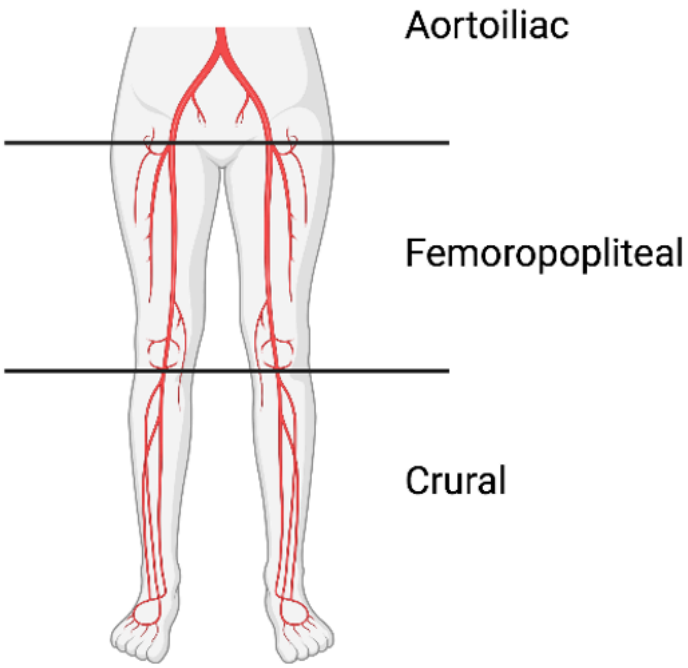
compared to those with diabetes or PVD alone at 26% (Pourghaderi, Yuquimpo, Roginski Guetter, Mansfield, & Park, 2020).

1.4.3.3 The pathogenesis of peripheral vascular disease

As for people without diabetes, atherosclerosis is the main driving factor in PVD. Through the pathways discussed, people with diabetes have a greater propensity for developing atherosclerosis combined with diffuse calcification of the vasculature. In T2DM, vascular abnormalities are often present prior to diagnosis. Their severity increases with the duration of disease and with poor glycaemic control The presence and severity of the complication educing pathways in diabetes contributes to an increased plaque burden, greater plaque instability and ultimately a greater complexity of PVD disease than when PVD is present in isolation. (Thiruvoipati et al., 2015).

The mechanisms involved in plaque formation and calcification have been already described. Atherosclerosis in patients with PVD and diabetes occurs in a different pattern to that seen in the population with PVD alone. The location of arterial disease is divided into aortoiliac, femoropopliteal or crural disease (Figure 1.3). In diabetes, plaque formation is more diffuse, often spares proximal vessels and there tends to be a greater propensity for atherosclerotic deposition in infrapopliteal segments (Thiruvoipati et al,. 2015) and narrowing of distal arteries. There is inhibition of arterial remodelling and poor collateral development leading to greater disease severity at presentation. This can also cause technical difficulty in management of the disease, as will be discussed later in this chapter. This disease pattern is due to the metabolic abnormalities seen within the vascular system in diabetes. High levels of von Willerbrand factor, plasma fibrinogen and abnormal platelet adhesiveness along with inhibition of the synthesis of prostacyclin and high LDL and VLDL levels lead to the more diffuse pattern of occlusion.

Figure 1.3 Vascular anatomy of the lower limb



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There is an accelerated course of atherosclerotic disease across the entire vasculature. PVD is a marker for disease within renovascular, coronary and cerebrovascular beds. The seven year incidence of first time MI is 20.2% in the population with diabetes compared to 3.5% in the non-diabetic population (Haffner, Lehto, Rönnemaa, Pyörälä, & Laakso, 1998). The atherosclerotic plaques cause endothelial dysfunction and inflammation, and this is thought to contribute to diabetes effect as an independent risk factor for stroke and poor outcomes in CV events, such as in hospital mortality. Some of this risk can be mitigated by HTN control.

Along with being morphologically different, PVD is also microscopically different in diabetes. Microvascular changes seen in diabetes contribute to outcomes of PVD, including the proinflammatory state associated with hyperglycaemia and hyperinsulinemia (Paneni et al., 2013). CRP is often elevated and acts as a procoagulant tissue factor, chemotactic factor and leukocyte adhesion molecule. It inhibits the synthesis of eNOS synthase and impairs fibrinolysis

increasing the risk of atherosclerotic plaque formation. The hyperglycaemic state is pro inflammatory, as are the plaques themselves, of which there is often a greater burden.

The combination of oxidative stress and hyperglycaemia also leads to AGE formation. An increase in AGEs further up regulate pro inflammatory transcription factors which in turn decrease endothelial function, reduce NO production, encourage leukocyte migration into tissues with transformation into foam cells. The first step of plaque formation. The presence of AGE also propagates vascular calcification and AGE inhibitors have been shown to reduce calcification in vessels in rats. Vascular calcification occurs within different layers of the vasculature. Intimal calcification leads to vascular stenosis and ultimately poor end organ perfusion. Medial calcification causes smooth muscle and elastin dysfunction, this leads to increased vessel stiffness, reduced vessel compliance and a poor response to vasoactive stimuli. Pedal artery calcification has been demonstrated to be associated with nephropathy and retinopathy and vascular calcification burden on CT is a surrogate marker for atherosclerotic burden and has been shown to be associated with amputation risk, CV risk and mortality (Thiruvoipati at al., 2015).

In the absence of diabetes, atherosclerotic plaques are often more stable. Once a plaque forms, smooth muscle cells proliferate in the media and intima, depositing extracellular matrix to stabilise plaque. In diabetes, cell proliferation is reduced. Less smooth muscle cell remodelling occurs, along with an impaired synthesis of collagen, resulting in reduced plaque stability. There is also an increase in matrix protease enzymes which promotes the breakdown of collagen. (Thiruvoipati at al., 2015). Plaques become inflamed and unstable with leukocyte migration and this promotes plaque rupture and further increases thrombus formation. Ultimately there is an increased risk of plaque rupture, thrombosis and ultimately hypoxia.

Occlusion of small vessels occurs more readily in the presence of diabetes. This is a result of a thrombogenic state, platelet malfunction and an increase in vascular tone and pathological

vasoconstriction. There is increased permeability within small vessels, arterio-venous shunting, precapillary sphincter malfunction (Lepäntalo et al., 2011) with impaired response and regulation to vasodilatory stimuli including NO. There is also a loss of the vasodilatory response to pain when neuropathy is present. Neuroischaemia is the combination of neuropathy and PVD acting in synergy to reduce oxygen delivery (Lepäntalo et al., 2011).

Small vessels disease is a driver of neuropathy along with PVD. Glucose enters platelets independently of insulin. The presence of glucose, increases platelet adhesiveness by activation of PKC and decreased production of NO. This increases the expression of P-selectin, a platelet adhesion molecule, on the platelets surface. Platelets form and function is further altered in the hyperglycaemic state by an abnormal influx of calcium. This too promotes the blockage of smaller vessels. Increased platelet aggregation along with increased free radical production leads to capillary damage. There is a decrease in nutrient rich blood flow and venous pooling secondary to AV shunts and sphincter malfunction. This results in warm dry skin, increasing propensity of skin breakdown and when an ulcer develops near an area of underlying digital artery disease this can lead to complete occlusion of digital collaterals and resultant gangrene.

The prothrombotic state is worsened by elevated blood viscosity and fibrinogen production. Along with a greater burden of small vessel disease, these factors contribute to greater restenosis rates post revascularisation. (Thiruvoipati et al, 2015). Changes within the microvasculature in people with diabetes and PVD are not fully resolved after revascularisation (Beckman et al., 2013) and the combination of microvascular and macrovascular damage impair perfusion of the limb and contribute to poor wound healing despite revascularisation.

1.4.3.4 The management of peripheral vascular disease

The diagnosis of PVD in diabetes can be difficult as the usual screening modalities may be less accurate. Non-invasive diagnosis includes the use of ultrasound doppler to identify flow through

vessels and ABPI, the ratio of systolic blood pressure between the ankle and arm. In diabetes, APBI can be inaccurate as the distal vasculature including the anterior tibial artery is more likely to be calcified. This gives deceivingly high readings. Charles et al (Charles et al., 2011) demonstrated an increased risk of ulceration at the same level of claudication as measured by ABPI in patients with diabetes when compared to the patients with PVD alone. This can be mitigated through the use of the toe brachial pressure index, but guidelines are not as clear, with no widely accepted measurement for PVD, and less practitioners are trained in its use. Transcutaneous oxygen pressure (TcPO2) is an assessment to determine to oxygenation of the skin surface; the poorer the flow to the tissues, the greater the severity of PVD. In diabetes, this measurement may be skewed due to venous pooling and are unreliable in the presence of neuropathy, oedema, infection or smoking, factors often present in the population with diabetes (Beckman at al., 2013). There can also be issues in assessing tissue vasculature due to the presence of callus (Beckman et al., 2013). Along with delays in diagnosis, the disease is often severe at presentation in diabetes. This is due to the propensity for asymptomatic disease and the reduced frequency of claudication symptoms. At time of presentation, options for treatment, specifically revascularisation is often limited. Options for revascularisation are further limited by the diffuse pattern of disease. Outcomes are poorer due to co-morbidities such as nephropathy and neuropathy, biochemical abnormalities and an increased risk of infection (Paneni et al., 2013).

The treatment of PVD can be classified as non-invasive and invasive management. Non-invasive treatment is based around lifestyle interventions and medical management (Jaff et al., 2015). Invasive management is further subdivided into surgical and endovascular interventions. The choice of intervention is dependent on patient, limb and lesions factors. The overall condition of the patient, the haematological status of the limb and the desired outcome of the procedure i.e limb salvage, improvement in function or treatment of symptoms must be considered. There is some disagreement as to when the severity of PVD reaches a threshold appropriate for treatment. The International Working Group on the Diabetic Foot (IWGDF) recommend non-interventional treatment if ABPI >= 0.6, TcPOs >=50mmhg or Toe Brachial pressure index (TBPI)

>= 55mmhg. At this level they recommend optimisation of risk factors with smoking cessation the main focus of management. If an ulcer is present, offloading of the ulcer is recommended along with debridement and treatment of any infection. Offloading involves reduction of the abnormal pressure through the ulcerated area, primarily through the use of casts and walkers (Baker & Osman, 2016). If no response is observed at 4-6 weeks then interventional therapy is recommended. If PVD is severe ABPI <0.6, TcPOs <50mmhg or TBPI <55mmhg and a foot ulcer is present, interventional therapy is recommended. For all guidelines revascularisation is recommended for patients with symptomatic disease, even with diabetes, as long as the lesions are amenable to treatment (Schamp et al., 2012). With regards to lesions, 30-50% foot ulcers are gangrenous at the time of presentation, which can be too late to successfully revascularize (Lepäntalo et al., 2011).

It is important to treat both the arteriosclerosis and microvascular complications concurrently to obtain adequate outcomes and the first step in treatment involves management of risk factors. Controlling smoking, reducing BMI, HTN and hyperlipidaemia reduce PVD risk and all-cause mortality as many of the micro and macrovascular complications are driven through the same pathways (Beckman et al., 2013). Statins have been shown to stabilise plaques and reduce limb loss (Kokkinidis et al., 2020), along with the risk reduction secondary to management of hyperlipidaemia (Beckman at al., 2013). This is thought to be due to the pleiotropic effects of statins, improving endothelial and microvascular function, remodelling, and stabilisation of plaques, increasing nitric oxide bioavailability and inhibition of the inflammatory response responsible for plaque instability (Calabr. & Yeh, 2005). ACE inhibitors have been demonstrated to improve cardiovascular risk but have no effect on amputation free survival (Huysman & Mathieu, 2009). It is unclear as to whether treating the risk factors in patients with diabetes and PVD improves outcomes; Charles et al (Charles et al., 2011) demonstrated no difference in amputation free survival after aggressive risk factor management in diabetes. There are also options for treatment that induces angiogenesis (Iyer & Annex, 2017), for example, cell therapy which enhances vascular growth factors to ischaemic tissues, although double blind placebo-controlled trials have not had convincing outcomes (Beckman at al., 2013).

Lifestyle modifications are focused on diet and structured exercise programmes. Exercise is recommended as the first line therapy by NICE for PVD if critical limb ischemia is not present. The evidence for the use of exercise in the management of PVD is unclear with many of the studies poorly defining populations and interventions (Zakari et al., 2018), but the evidence suggests that exercise programmes are less effective in diabetes. This is felt to be due to a reduced ability for vascular remodelling. Despite this exercise programmes still form a cornerstone of management and have been shown to correct metabolic abnormalities through changing the oxidative capacity of SM, the distribution of blood flow and increasing the utilization of oxygen in tissues in some populations. (Tan, 2000).

Interventional treatments can be endovascular (percutaneous) or surgical. Endovascular revascularisation is divided into two types, angioplasty in which segments of a vessels are stretched with a balloon over a wire and stenting in which a material is inserted to provide radial force to keep a vessel patent. There are also two types of surgical revascularisation. Endarterectomy in which a plaque is removed or bypass in which where a blocked segment of vessel is passed by a conduit. Conduits can be either native tissue or prosthetic. Native vein conduits are associated with better outcomes and with reduced infection risk. This is important in the diabetes population as the risk of infection is higher (Beckman at al., 2013). The decision as to which intervention is utilised is dependent on comorbid conditions, disease severity and the extent of the lesion. Intervention should only be attempted if the lesion is amenable, there is no irreversible gangrene and the patient is likely to survive the procedure (Thiruvoipati et al., 2015). If the patient is suitable, early revascularisation is necessary to reduce the risk of future amputation and further investigation within six weeks is required if an ulcer is not healing (Lepäntalo et al., 2011), even if original imaging demonstrated mild disease (WGDF-PAD, 2011).

The only study examining outcomes following endovascular vs open procedures, Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL), was in a mixed population of diabetes and

non-diabetes patients. Forty two percent of patients had diabetes, but no subgroup analysis was performed. The study focused on femoropopliteal lesions; a pattern of disease less commonly seen in diabetes. BASIL II is currently underway examining infrapopilteal lesions, the pattern of disease more commonly seen in diabetes. Endovascular bypass was found to be less morbid and was less costly but had equal outcomes for quality of life. If patients survived beyond 2 years there was greater overall survival but no significant difference in amputation free survival in those that underwent open bypass. There is a greater risk of requiring a secondary revascularisation procedure in diabetes. Surgery following a failed endovascular procedure has a significantly higher mortality than if primary surgery had been performed (Bradbury et al., 2010) and there is some evidence to suggest that ulcer healing is greater in people with diabetes if surgical revascularisation is initially performed (Paneni et al., 2013). In patients with diabetes, worse outcomes for endovascular procedures have been demonstrated when compared to the general population along with a higher morbidity following procedures and patients are less likely to be technically suitable for angioplasty due to the length of diseased vessel involved (Beckman at al., 2013). Outcomes of surgical peripheral artery reconstruction are broadly similar to the general population unless there is severe neuropathy and there is no current evidence to suggest vein graft patency is poorer. One-year amputation free survival is 76% after revascularisation in patients with diabetes and critical limb ischemia for both endovascular and surgical procedures and ultimately there are better outcomes if there is no delay to revascularisation (Thiruvoipati et al., 2015). However, a large meta-analysis demonstrated that after revascularisation people with diabetes are more likely to be admitted to hospital and have an increased risk of post procedure complications (S. L. Smith, Matthews, Moxon, & Golledge, 2019). With a multitude of changes occurring within the vasculature, when revascularisation occurs outcomes are less predictable than in the general population (Beckman at al, 2013).

Immediate outcomes following revascularisation can be affected by the presence of chronic kidney disease, especially if there is a requirement for dialysis, if foot gangrene is present or if it was an urgent procedure. Patients with diabetes undergoing revascularisation are more likely to have co-morbidities at the time of revascularisation (Lepäntalo et al, 2011). Systemic

complications, such as MI, occur in around 10% of patients. After surgical intervention perioperatively mortality is small but increases over time to reach 40-50%, near pre-operative rates, after 5 years. Long term data is not yet available for endovascular repair (Lepäntalo et al, 2011). Despite the initial risk of endovascular or surgical revascularisation, better survival outcomes are seen in those that undergo revascularisation procedures than in those that require an amputation as a first line treatment option. Not undergoing an interventional procedure is an independent risk factor for amputation and mortality (Faglia et al., 2009; Jude, Eleftheriadou, & Tentolouris, 2010). Chronic limb ischaemia is associated with a 50% mortality at 6 months if a patient is not suitable for revascularisation. The presence of ESRD and CAD further increase mortality (Lepäntalo et al., 2011).

With the disease pattern present in diabetes, distal surgical revascularisation procedures are often required. Compared to the more frequently performed proximal ilioaortic and femoropopliteal procedures, they have greater risks and are technically more difficult. Over 20% of patients, with or without diabetes, will require amputation within 1 year of the procedure and there is greater post procedural mortality in patients with diabetes. Infrapopliteal lesions are more difficult to treat due to a longer lesion length, the severity of calcification making anastomosis more challenging and smaller vessel diameter (Schamp et al., 2012). It is particularly important to use veins for bypass as there is also a greater rate of prosthetic graft failure if a native vein conduit cannot be used (Vartanian Shant & Conte Michael, 2015). As it is a more technically difficult procedure and as less are being performed due to the increase in endovascular procedures access is an issue as there are fewer numbers of providers that can perform the procedure. Endovascular treatment is becoming more popular for infrapopliteal lesions. The aim of the procedure is to achieve at least one vessel infrapopliteal arterial flow to the foot. There is discord within the literature as to whether three vessel flow should be restored or whether one is sufficient and there is currently no consensus (Lepäntalo et al., 2011). Endovascular procedures within distal segments are also more technically challenging. There are greater rates of wire recoil, vessel dissection and restenosis (E. J. Armstrong, Bishu, & Waldo, 2016; Nakamura et al., 2003; Paraskevas, Baker, Pompella, & Mikhailidis, 2008) The outcomes

after endovascular intervention may also be dependent on the diabetic milleu at the time of procedure. The hyperglycaemia millue reduces the likelihood of treatment success. In the population with diabetes after interventional therapy an estimated 60% of patients will achieve wound healing at 1 year, 40% will undergo disease progression and some will require amputation even despite a patent graft. Multiple attempts at revascularisation may be required. The cardiovascular Effects of Ticagrelor and Clopidogrel in Patients With Peripheral Artery Disease (EUCLID) trial demonstrating a 14.2% increase of major CV event post procedure associated with every 1% increase in HbA1c (Low Wang et al., 2018)

However, patients can heal without revascularisation, in one large study wound healing occurred in 50% of patients with severe PVD and diabetes without any attempt at revascularisation (Paneni et al., 2013). The complexity in the management of PVD in patients with diabetes highlights the importance of multidisciplinary team (MDT) working.

1.4.4 Infection

There is a relative immunodeficiency associated with diabetes (Noor, Khan, & Ahmad, 2017), which in combination with neuropathy and ischaemia leads to an increased risk of lower limb infection and ulceration. Infections are defined as the presence of multiplying bacteria in body tissues, resulting in cellular injury (White, Cooper, & Kingsley, 2001) and a diabetic foot infection is classified as any superficial or deep infection below the malleoli (Mandell et al., 2018). They can range from uncomplicated, affecting only a localised area, to necrotising fasciitis and if untreated, death. When infection is present in the foot, especially in the presence of ulceration, the risk of amputation is greatly increased. This risk is even greater if PVD is present, this is particularly concerning in that neuroischaemic ulcers are most susceptible to infection (Apelqvist, 2008). Infections most commonly occur as a consequence of ulceration but can present independently as cellulitis or secondary to other traumatic wounds including after operations.

1.4.4.1 The burden of infection

Due to the variance in severity, presentation and documentation of infections the exact incidence and prevalence of diabetic foot infections is difficult to ascertain. As in PVD, classical signs of infection within the foot, erythema, oedema, rubour, tenderness and pain, are often not present in diabetes. There can be a dulled inflammatory response, a reduced perception of pain and the local and systemic response is reduced in the hyperglycaemic state (D. T. Williams, Hilton, & Harding, 2004). In almost 50% of cases where deep infections is present, common signs such as raised white blood cell count (WBC), erythrocyte sedimentation rate (ESR), CRP and fever are absent, leading to delayed and missed diagnosis (B. A. Lipsky, Berendt, Embil, & De Lalla, 2004). The systemic response is often obscured by PVD, neuropathy and immunological dysfunctions. Other signs are common such as malodour, poor granulation tissue and delayed healing. Pain especially in the presence of neuropathy is a red flag for infection.

The incidence of foot infection is much greater in persons with diabetes compared to the general population. There is a 4% lifetime risk of foot infection in the general population but a 4% annual risk with diabetes (E. Peters & Lipsky, 2014). Over the lifetime of disease, the risk of developing a foot infection is estimated to be as high as 25% (Uçkay, Aragón-Sánchez, Lew, & Lipsky, 2015). In a large population cohort study of 104,717 patients attending primary care practices within the UK there was a markedly increased incidence of bone and joint infection and cellulitis in the population with diabetes with incidence rate ratios of 4.47 and 1.38 respectively. Unfortunately, the study did not determine location of infection(Carey et al., 2018).

The need for hospitalisation is also greater once infection occurs. The risk of hospitalisation with any infection of the lower limb is 10 times greater in diabetes and there is a strong association between worsening glycaemic control and requirement for hospital admission (Critchley et al., 2018). Infection can also lead to worsening of diabetes control, initiating a cycle of poor wound healing. Outcomes of infection in diabetes are related to the depth of tissue involvement, patient comorbidities and the presence of PVD (Lepäntalo et al., 2011) and once infection has developed, it's presence substantially increases the risk of amputation. Deep infections are present in around

25-50% of amputations (Bandyk, 2018) and of those patients admitted with a lower limb infection, 50% will go on to require an amputation; 10% of which will be major (Sen, Demirdal, & Emir, 2019). If infection is present with concurrent PVD, urgent intervention is required leading to Diabetes UK pushing the campaign 'time is tissue'(Diabetes UK, 2015c).

1.4.4.2 The risk factors for infection

Unlike for PVD and neuropathy, risk factors for diabetes foot infections are less well defined in the literature. As discussed, worsening glycaemic control is strongly associated with the presence of infection and poor outcomes from infection including hospitalisation and death (Critchley et al., 2018; Pearson-Stuttard, Blundell, Harris, Cook, & Critchley, 2016; Peleg, Weerarathna, McCarthy, & Davis, 2007). Anything that causes a break in a skin barrier, allowing invasion of microorganism, will increase the risk of infection. That can be mechanical or thermal trauma, or ulceration (Noor et al., 2017). Changes to the foot architecture and pressure or degradation of the skin barrier such as that caused by neuropathy and PVD, therefore increase the risk of infection. Other risk factors associated with foot infection have been noted such as barefoot walking, low socioeconomic status, illiteracy and a delay in presentation with wounds and ulcer, however the evidence is often from smaller studies and can be contradictory (Noor et al., 2017; E. J. Peters, Lavery, & Armstrong, 2005). In a large prospective study of patients attending an outpatient clinic, all but one of the 151 foot infections that occurred were secondary to a foot wound. Risk factors significantly associated with foot infection in the study included long standing wounds (>30 days), recurrent wounds, trauma and wounds that penetrated to bone (Lawrence A. Lavery et al., 2006). This is in keeping with other studies demonstrating an increased risk of infection in those with a history of previous amputation (Hobizal & Wukich, 2012).

1.4.4.3 The pathogenesis of infection

Wound healing has defined and orderly phases. In diabetes, where there is sustained hyperglycaemia and chronic elevation of pro-inflammatory markers (Tellechea, Leal, Veves, &

Carvalho, 2010), every stage of healing is affected. Wound healing is impaired due to a number of extrinsic factors such as an increased risk of skin barrier break down and a multitude of intrinsic factors. As discussed previously, there is a chronic low grade inflammatory state, driven by elevated pro-inflammatory mediators which is low grade due to the impairment of cellular defence mechanisms by hyperglycaemia. The combination of a low grade inflammatory state and the poor function of cellular defence mechanisms leads to an ineffective and prolonged inflammatory reaction in wounds. There is alteration in macrophage function, with a reduced ability to support tissue regrowth and a propensity to encourage apoptosis and inflammation (Khanna et al., 2010; Okonkwo & DiPietro, 2017). Macrophages are a key source of pro-angiogenic factors including vascular endothelial growth factor (VEGF) in wounds, and the decrease in function and volume of macrophages contribute to the poor angiogenesis seen in diabetic wounds(Okonkwo & DiPietro, 2017). Abnormal angiogenesis plays a role in most micro and macro vascular complications of diabetes and poor angiogenesis is a contributing factor in diabetic foot infections. Ultimately, poor perfusion of wounds leads to impaired healing and recurrent ulcer formation.

The hyperglycaemia state also affects the phagocytic and bactericidal activities of neutrophils, further increasing the susceptibility to infection (Alba-Loureiro et al., 2007). There is increased T lymphocyte apoptosis which inhibits healing (A. K. Arya, Tripathi, Kumar, & Tripathi, 2014). In addition, there is a reduction in bone marrow synthesis of endothelial progenitor cells. Endothelial progenitor cells are a multitude of cell types involved in neovascularization (Yoder, 2012). The deficit and abnormal function of these cells reduces vascularity in normal tissues and reduces capillary growth, collagen deposition and the development of granulation tissue within wounds further impairing healing (Okonkwo & DiPietro, 2017). This increases the duration of ulceration and abscesses, increasing the opportunity for bacteria to enter. The deficit also impairs the synthesis and function of other factors required for wound healing.

As expected, the most common pathogens found in diabetic foot infections are those commonly found in skin flora, staphylococcus aureus and beta-haemolytic streptococci along with gram negative bacterium pseudomonas aeruginosa and Escherichia coli, Staphylococcus aureus is the most common pathogen. If the wound has been present for a prolonged period there is a greater chance that anaerobic gram negative organisms will be identified within the wound along with gram positive organisms. Obligate anaerobes are more commonly found in necrotic and gangrenous wounds due to the lack of oxygenation of the tissue. Infection with multiple microbes is common as is infection with resistant strains such as methicillin-resistant staphylococcus aureus (MRSA). MRSA have been shown to be identified in 30-40% of ulcers, associated with the recurrent and prolonged antibiotic use which is often required for treatment of ulcers. Resistant bacteria are associated with an increased risk of amputation (Bandyk, 2018).

One of the most severe outcomes of Infection is OM (Mandell et al., 2018). It is estimated that 15% of people with a diabetic foot ulcer will develop this. Acute, subacute and chronic variations are seen. Acute is often defined as the presence of symptomology for less that 10-14 days, subacute less that 3 months but without the symptoms of acute disease and chronic is greater than this. Chronic OM occurs with the development of an area of bone necrosis. This often develops into a surrounding sclerotic hypo-vascular bone, thickened periosteum with changes to surrounding soft tissue (Mandell et al, 2018). OM is not the only bony change seen in the foot in diabetes. Avascular necrosis, osteochondritis and fracture occur more frequently than in the general population. Septic arthritis is commonly identified, with 33% of all feet imaged showing concurrent disease (Mandell et al., 2018).

1.4.4.4 The management of infection

As for neuropathy and PVD management of foot infection is based around severity. The diagnosis of infection is clinical, with severity assessed through classification guidelines. This requires performing a clinical assessment of the patient and foot, debriding and assessing the depth of the wound and assessing arterial perfusion (Benjamin A Lipsky et al., 2016; NICE, 2016). Infection

is classified into mild, moderate and severe based on localised and systemic signs and symptoms, Table 1.1, and treatment is tailored to severity and pathogen. The determination of severity influences the method and length of administration of antibiotics, the requirement for hospitalization and the need for invasive management such as surgery (Benjamin A. Lipsky, 1999).

Table 1.1 IWDGF classification systems for defining diabetic foot infection. Modified from IWGDF guidance on the diagnosis and management of foot infections in persons with diabetes(Benjamin A Lipsky et al., 2016)

Severity	Clinical findings
1 - Uninfected	Absence of local or systemic signs or symptoms of infection
2- Mild	+ ≥2 of: - Swelling or induration - Erythema >0.5 cm around the wound but less than <2cm - Local tenderness, pain or warmth - Purulent discharge + Infection involving only the superficial tissues + No systemic symptoms or signs
3 - Moderate	+ Infection involving deep structures - bone, joint, tendon or muscle or + Erythema extending ≥2 cm from wound edge + No systemic symptoms or signs
4- Severe	+ Any foot infection with SIRS, ≥2 of: - HR >90 bpm - RR >20 breaths/min - Temperature >38 °C or <36 °C - PaCO2 <4.3 kPa (32 mmHg) - WBC <4 or >12 g/l

SIRS: Systemic inflammatory response syndrome; HR: Heart rate; BPM; beats per minute; RR: Respiratory rate; WBC: white blood cell count

X-rays are recommended to assess the extent of disease but there should be a high suspicion for OM as it can be present with normal x-rays and cultures (Benjamin A Lipsky et al., 2016). If there is any suspicion there should be a low threshold for MRI (NICE, 2016).

Once infection is identified, empirical antibiotics should be initiated. To tailor the treatment, NICE and IWGDF guidelines recommend sampling the soft tissue or bone for microbiological investigation. If this is not possible a deep wound swab can be used to identify pathogens (Benjamin A Lipsky et al., 2016; NICE, 2016). It has been the general consensus that tissue sampling has greater reliability as swabs are more likely to be contaminated by skin flora and may not identify the specific pathogen responsible for infection. This stance was recently confirmed by a large UK based prospective study that demonstrated more pathogens and less contaminates from tissue sampling compared to swab samples(Nelson et al., 2018). This is of particular importance in neuroischaemic and deep wounds where swabs have been found to be less accurate(Demetriou et al., 2013; Huang et al., 2016).

If an infection is determined to be severe hospitalisation is required for IV antibiotics, resuscitation and glycaemic control (NICE, 2016). There may be a need for invasive management such as surgery. If a patient has erythema and swelling with overlying gangrene or other reasons to suspect a deep infection, there should be a low threshold for surgical wound debridement and exploration for an abscess. Surgical debridement is preferred over topical debridement but there is no published evidence adequately powered to compare outcomes (Elraiyah et al., 2016; Lawrence A Lavery et al., 2016). Although debridement is the main stay of treatment (Everett & Mathioudakis) the volume of published evidence is small with a few small trials (Elraiyah et al., 2016; Game et al., 2016; Sumpio, 2012) and some indirect evidence (Taylor & Porter, 1987; Tennvall, Apelqvist, & Eneroth, 2000) to support its use. NICE recommend debridement is only performed by practitioners qualified in its use as It requires a skilled operator. An important role for MDTs, to get expedient access to the most appropriate specialities for management. If OM is present, management can be conservative or surgical but antibiotic penetration to avascular tissues is poor and amputation may be required (Mandell et al, 2018).

Revascularisation is important to improve blood flow to allow for successful healing, but timing is important. If infection with an abscess is present it is important to drain and debride the foot first and delay revascularisation by 2-5 days to allow time for infection control. Simultaneous revascularisation can occur, preferably endovascular if sepsis is present to allow maximal blood flow to sites. The outcomes of minor amputation prior to bypass are worse than if revascularisation is performed first. Multiple debridement's and months of treatment are often needed for the infection to clear and for an ulcer to heal if present even after successful revascularisation (Lepäntalo et al., 2011).

1.4.5 Foot ulceration

The most common manifestation of diabetic foot disease is a foot ulcer. Ulceration affects all layers of the epidermis and can culminate in necrosis or gangrene. Risks of ulceration are well documented and include previous lower limb ulcer or amputation, anatomic foot deformity, PVD, neuropathy, ESRD with a particularly high risk in those persons requiring dialysis, poor glycaemic control and smoking (Aumiller & Dollahite, 2015; B. A. Lipsky et al., 2012). Ulcer risk is increased 32 fold if a foot deformity, neuropathy or previous amputation is present(Bandyk, 2018). In one of the larger prospective studies looking at ulceration risk factors, a concurrent ulcer at baseline, a history of ulcer, abnormal neuropathy and previous podiatry attendance, reduced pulses, foot deformity and abnormal ankle reflexes along with age were positively associated with presence of ulcer (Abbott et al., 2002). The immune changes previously discussed reduce the chance of healing once ulcer develops.

As with infection, accurate estimation of diabetic foot disease is complex as foot disease many not progress to a severity reviewed within a care setting and there is a lack of standardisation in coding of the diabetic foot including ulceration. Fifteen percent of people with diabetes are expected to develop foot ulcers over the lifetime of their disease. The estimated lifetime incidence is as high as 68 per 1,000 persons (Aumiller & Dollahite, 2015). The burden of disease

is expected to rise as the main contributing factors to diabetic foot disease continue to increase. Neuropathy and PVD are present in more than 10% of people with T2DM at the time of diagnosis (Boulton, Vileikyte, Ragnarson-Tennvall, & Apelqvist, 2005) and 10% percent of patients who present with an ulcer are previously undiagnosed with diabetes (Abbott et al., 2011). Neuropathy as a co-morbidity increases the annual risk of ulceration to 7-10%. If this is associated with PVD, a previous ulcer or amputation the risk more than doubles to 25-30% (Lepäntalo et al., 2011). One ulceration develops the risk of amputation markedly elevates with 5-8% of patients requiring a major amputation within the following year.

Ulceration presents in three forms; neuropathic, ischaemic and neuroischaemic. Neuropathic ulcers occur when there is neuropathy alone. They present as a warm perfused foot with dry cracked skin. Ischaemic ulcers occur when there is PVD without neuropathy and present in a cold, painful foot. Between 10-60% of ulcers have an ischemic origin, whether mixed or simple (N. Ahmad, Adderley, Ionac, & Bowling, 2019). Mixed neuroischaemic ulcers occur in the presence of both PVD and neuropathy, present in a cold painless foot and are the most common type, responsible for around 80% of diabetes ulceration.

Understanding the causative aetiology of the ulcer is important as it affects management and outcomes. It is difficult to rule out an ischaemic limb without adequate investigation as clinically a devascularised neuropathic foot may appear pink and well perfused due to AV shunting. A capillary refill of greater than 5 seconds or delayed discoloration of the foot can indicate poor flow but can be easily missed unless one has a high index of suspicion. As discussed previously, common bedside tests used for the determination of PVD are not as accurate in the presence of diabetes. ABPI is not accurate in up to 35% of patients (B. A. Lipsky et al., 2004) and in 16% of patients TBPI cannot be used due to the presence of gangrene or previous amputation (Bandyk, 2018).

The current policy in place in Wales for management of diabetes and its complications is the Diabetes Delivery Plan for Wales 2016– 2020, which proposes preventative foot-care strategies such as support of screening programmes, education and improved access to healthcare as well as mandated participation in the national diabetes audit(NHS Digital, 2018; NICE, 2016). The national diabetes audit is an essential source of data used to target improvements in service delivery and for estimation of the burden of disease (Hillson, 2016). Despite this participation has reduced, resulting in a potential failure to capture an accurate screenshot of diabetic foot disease in Wales (Diabetes UK, 2015b).

1.4.5.1 The management of foot ulceration

The treatment goal for management of the diabetic foot is to allow tissue healing while maintaining adequate function, weight bearing and ambulation (Bandyk, 2018). There needs to be a multifactorial aggressive approach to address both ischemic and infective issues whilst simultaneously addressing glycaemic control. Maintaining adequate glycaemic control can be difficult in the presence of infection and the introduction of insulin may be required. Hyperglycaemia provides an environment for proliferation of infection. It is associated with poor ulcer healing (Marston, 2006), increased recurrence rates, poor operative outcomes along with morbidity and mortality (Muntner et al., 2005).

Protocol driven care provided by an MDT is necessary for the proper treatment of ulceration. In the most recent report from the national diabetes audit, a large prospective UK audit comparing services to NICE guidelines, there was an association identified between MDT, shorter wait times for ulcer review and being alive and ulcer free at 12 weeks(NHS Digital, 2018). Treatment is focused around managing infection, removal of necrotic tissue, offloading and adequate perfusion. This is in combination with patient education and the use of adequate footwear. If vascular abnormalities are noted, referral to vascular centres should happen expediently, especially as they are now centralised within the UK. Vascular imaging should be implemented conservatively in the acute setting and only used if strategic, to avoid delays in management and

overwhelm of tertiary centres (Lepäntalo et al., 2011; Pomposelli, 2010). For this to occur successfully there needs to be clear protocols and guidelines on referral within each health board as it is an area in which patients can be lost to follow up. The European society of vascular surgery and NICE recommend early revascularisation for neuroischaemic ulcers as neuropathy further impairs healing (Lepäntalo et al., 2011). After revascularisation 50-60% of ulcers are healed at 20 weeks but wounds will take longer to heal after revascularisation in patients with diabetes and the completeness of revascularisation is important. Other co-morbidities will also affect wound healing. ESRD has been found to be an independent predictor of non healing foot lesions, highlighting the importance of a holistic approach to managing these patients (NHS Digital, 2018).

Offloading is important for ulcers with a neuropathic element. It involves reduction of the abnormal pressure through the ulcerated area. This allows for an increase in blood supply and a reduction in further traumatic forces on the area. Total contact casting is the gold standard for offloading (NICE, 2015). It can reduce pressure on the wound and has been shown to produce healing in 73-92% ulcers (Elraiyah et al., 2016(b); Messenger et al., 2018). It is not utilised in all units as it requires a level of skill, time and resources and can be poorly tolerated by patients due to its restrictive nature (Bus, 2016). Complications include irritation from the plaster and difficulty in serially assessing the injury. Another option which allows for more frequent inspection and is more readily available is the removable walker. As these are easily removable, adherence to the therapy can be lower and they have been found to be less effective at ulcer healing than total contact casting (IWGDF, 2019b). Treatment is also site specific and if abnormal pressure persists, such as on the plantar foot surface the metatarsal head is usually the problem and this may require bone or joint resection to allow for full skin healing (Finestone, Tamir, Ron, Wiser, & Agar, 2018).

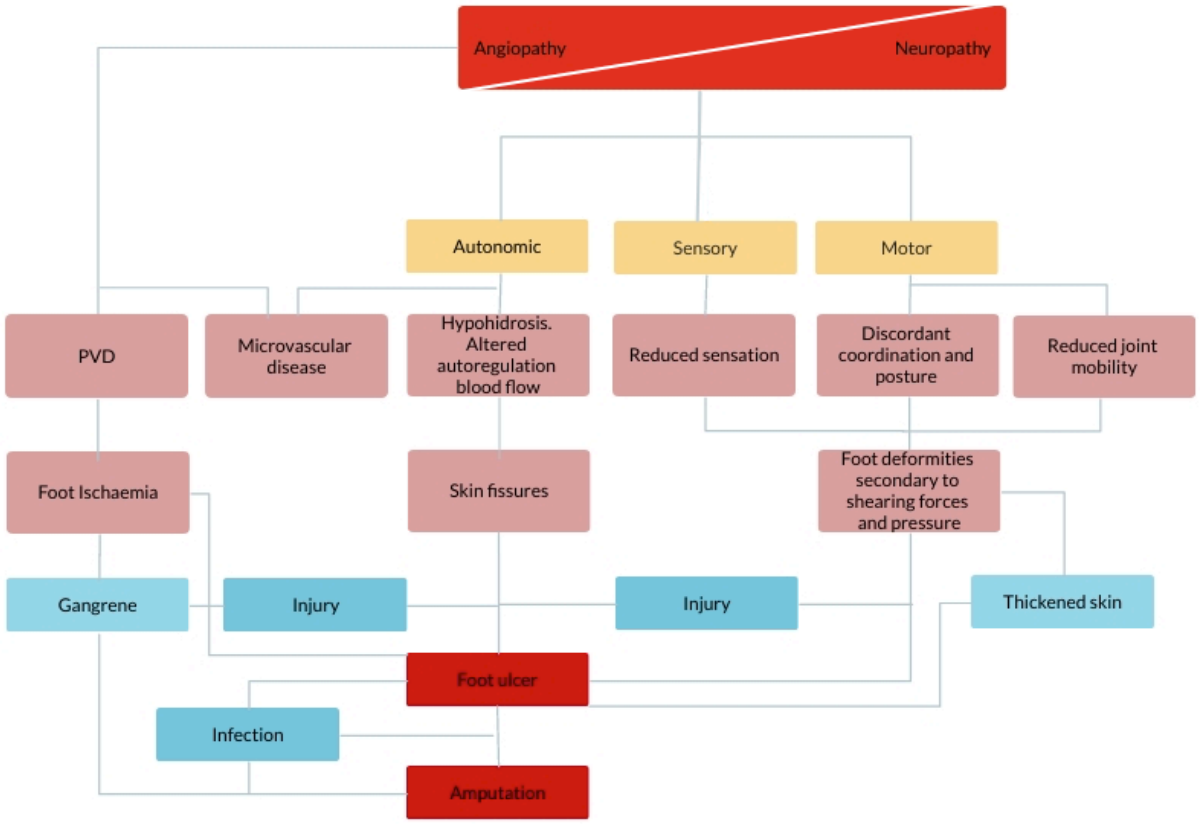
Ulcer healing varies by location with heel ulcers slower to heal than plantar ulcers. The largest prospective epidemiological study of diabetic foot disease within the UK was started in 2014. The

national diabetic foot care audit has followed over 20,000 ulcers between 2014-2017. At 12 weeks less than half of all ulcers (48%) had healed. Healing rate was dependant on severity with 1 in 3 severe ulcers (34%) and 3 in 5 less severe ulcers (60%) healed at 12 weeks and an association was identified between heel ulcers and poorer healing rates. One in 40 cases (2.5%) were followed by death within 12 weeks and 3% of patients with severe ulceration went on to require major amputation (NHS Digital, 2018).

1.5 Amputation

Diabetes is the primary underlying cause of non-traumatic amputation in the UK (P. W. Moxey et al., 2010a) and worldwide (International Diabetes Federation, 2019). Within the UK people with diabetes are 9 times more likely than those without to undergo major amputation. In foot infection and ulceration, amputation can be urgent or curative and either life or limb preserving but is ultimately the last step in a progressive disease process (Figure 1.4). Amputation prevention is complex and requires a holistic approach, addressing the multitude of underlying pathways. Fortunately, in the most optimistic models, it is believed that up to 80% of amputation is preventable with adequate management through an MDT approach. Recurrence rate after primary amputation are as high as 50% (Boulton et al., 2005). Lifetime risk of foot ulceration for diabetic patients is up to 25% and this burden is expected to increase as the main contributing factors to diabetic foot disease continue to rise with neuropathy and PVD present in more than 10% of people with T2DM at the time of diagnosis.

Figure 1.4 Common aetiological pathway of diabetes related foot disease. Modified from the international working group on the diabetic foot, international consensus on the diabetic foot 1999 (IWGDF, 2019a).



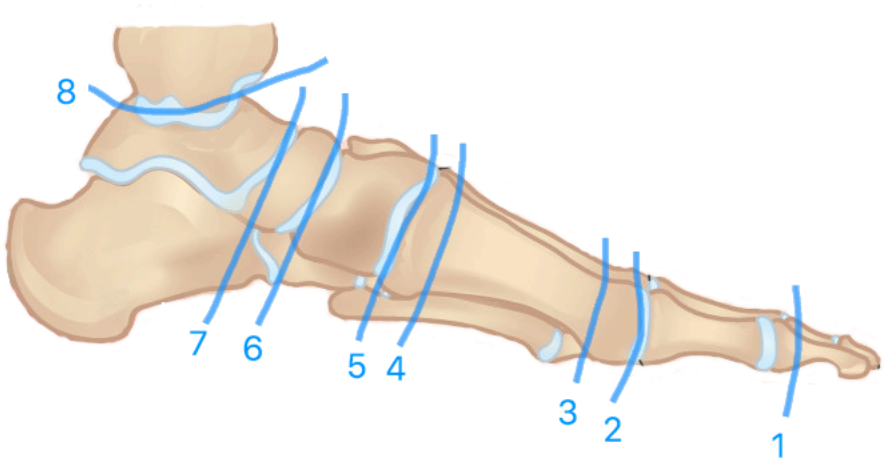
PVD; Peripheral Vascular Disease

1.5.1 Amputation types

There are consecutive levels of lower limb amputation that can be performed dependent on the situation. Ideally the lowest level of amputation that will allow healing is chosen but there are a number of patient and limb factors that would require major amputation. In an emergency situation when mobility is not important, such as when the patient is bedridden or has poor prior ambulation that would not support a prosthesis/rehabilitation, if life expectancy is less than 1 year or revascularisation is contraindicated or unlikely to be successful major amputation is preferred to reduce the strain of potential recurrent surgeries.

Amputations are delineated into major and minor. Major amputations are those performed above the ankle joint and minor are any procedures performed below. Major lower limb amputations are viewed as an adverse outcome of diabetes and are associated with poor survival rates and a reduced quality and quantity of life. Minor amputations, those of the forefoot and toe, are often seen as a preventative procedure, encouraging tissue healing through removal of infected or necrotic tissue. The most common types of minor amputation are shown in Figure 1.5. Other, more proximal procedures are possible but are performed less frequently. They are proximal metatarsal (lisfranc), mid tarsal (chopart) and through ankle (syme), numbers 6-8 in Figure 1.5. Toe, ray and transmetatarsal amputations are preferred to allow a broad distribution of weight for mobilisation postoperatively. Amputation through the phalanges or disarticulation of the metatarsal phalangeal joints are the most common procedures performed. At any amputation level if infection recurs within a stump, if the level was not adequate to remove all infected or necrotic tissue or if blood supply is poor, stump breakdown can occur with the requirement for amputation at a higher level.

Figure 1.5 Level of transection in common minor amputations



1. Toe amputation 2. Toe disarticulation 3. Distal transmetatarsal amputation 4. Proximal transmetatarsal amputation 5. Tarso metatarsal disarticulation 6. Mid tarsal disarticulation 7. Intertarsal disarticulation (chopart) 8.Syme (Injurymap, 2019)

Despite minor amputations being viewed as a treatment, all amputations are associated with some adverse effects. Great toe and fifth toe amputations can affect balance and gait, and second toe amputation can lead to hallux valgus. Amputation of the second to fourth toes disrupts structural ligaments, affecting the anterior transverse arch of the foot (Nather & Wong, 2013).

The next level is a transmetatarsal amputation, or partial foot amputation. This procedure is usually performed where there is the presence of a forefoot wound or ulcers that cross interdigit boundaries. The procedure causes increased pressure in the dorsal contact area of the foot. This may result in further callus and ulcer formation. Gait and posture are negatively affected as the lever arch of foot is shortened but there is the option of prosthesis. A mid tarsal amputation can also be performed at the tarsometatarsal line, between the talus and calcaneus proximally and cuboid and navicular distally or an amputation at the ankle distally. These are mainly performed in children secondary to congenital malformations and again there is option for prosthesis. Further surgery may be required at a later date as stumps are prone to skin breakdown and joint pain (Nather & Wong, 2013).

Major amputations are procedures performed above the ankle with the most common procedures performed above knee (AKA) and below knee amputations (BKA). Through knee procedures are now performed rarely due to poor wound healing rates related to long tissue flaps and challenges with prosthetic fitting related to the femoral condyles (Morse, Cull, Kalbaugh, Cass, & Taylor, 2008). Choice of procedure is dependent on the amputation type that will give the best outcomes for the patient and on how secure the vasculature is. This can have significant consequences, so a number of factors are considered, including the boundary of necrotic or infected tissue. The procedure will fail, and further amputation may be required if residual infection is present or blood supply is poor causing failure of stump healing or stump breakdown. The suitability for prosthesis needs to be considered as ambulation is increasingly impaired with higher levels of amputation due to the length of lever. If a patient is expected to recover with the strength to mobilise post operatively then best efforts are made to perform the

most distal operation. A persons pre morbid level of mobility and function are considered and if patients are very frail, a decision may be taken to perform a more proximal amputation to reduce the burden of further surgery. (Dwars, van den Brock, Rauwerda, & Bakker, 1992).

BKA is division through the tibia and fibula with preservation of the knee joint. Preservation of the knee joint results in less energy expenditure being required to mobilise and for better proprioception than an AKA. There are also greater options for prosthesis allowing for a near normal level of function after rehabilitation. BKAs are associated with a decreased mortality and increased likelihood of mobility in the elderly population when compared to an AKA due to the reduced effort of ambulation (Physiopedia contributors, 2020). Post operatively, patients are at risk of knee flexion contractures and a bone bridge may be required if distal fibula pain develops, requiring further surgery. AKA is division through the femur. When performed it requires a significantly higher level of energy expenditure of around 60-110% to ambulate dependant on the length of the amputation stump.

The highest level of major amputation performed, albeit very rarely, is hip disarticulation. This is amputation of the whole limb through the hip joint and is usually performed secondary to trauma, tumour or severe infection. The risk of wound complication and mortality with this operation is very high (Physiopedia contributors,2020).

1.5.2 The burden of amputation

The most recent NICE guidelines 'Diabetic Foot Problems: Prevention and Management' have highlighted that levels of morbidity and mortality related to diabetes-related foot disease throughout the UK are unacceptably high. In addition to creating a significant financial impact, there is a marked variation noted across regions (NICE, 2016). The impact on morbidity and associated mortality for people with diabetes where foot disease progresses to the point of amputation is substantial (NICE, 2016). In people with diabetes, the median survival after

amputation of any cause has been reported to be 20 months shorter compared to people without diabetes (Fortington et al., 2013). Five-year mortality rates after amputation in people with diabetes are reported to be as high as 80% (Diabetes UK, 2015c). Even in those who develop foot ulceration but do not progress to amputation there is an approximate twofold increased risk of premature death (Scott et al., 2014). As well as the cost to the individual and their quality of life, the financial burden of amputation on a health board is considerable with the primary treatment episode of major lower limb amputation being approximately £40,000 (NICE, 2016).

Diabetes UK annual figures suggest that amputations secondary to diabetic foot disease are increasing and there were estimated to be greater than 300 procedures per year in 2015. In England amputation is 6 times more prevalent in the population with diabetes compared to the population without and 45% of the amputations in England are performed in people with diabetes. (Naseer Ahmad, Thomas, Gill, & Torella, 2016). There are currently no published figures related to diabetes amputation rates for Wales as a country and it is not known if there is variance between health boards. In the most recent state of a nation report by Diabetes UK, based on data from the diabetic foot audit, there was a significantly higher requirement for major amputation secondary to ulceration between England and Wales. As 84% of amputations are preceded by ulceration in diabetes it suggests the amputation rate is higher in Wales. This is needs to be clarified so that causative factors can be appropriately investigated.

This is not only an issue within Wales. The IDF in the latest edition of its atlas called for more robust epidemiological studies to understand the impact of diabetes. One area in which there is a sparsity of accurate and country specific data is ulcer and amputation rates. There is a lack of continuous longitudinal population-based data on lower extremity amputation (International Diabetes Federation, 2019) with disparity between and within countries as to whether rates are increasing or decreasing over time. Analysis of amputation procedures on an international level are complicated by data set incompleteness, differing administrative systems, and a relative lack of standardisation and utilisation of diagnosis and procedures internationally, along with

differences in definitions of side and site of amputation. Although amputation rates have been regularly reported using questionnaires and administrative data (Aljarrah et al., 2019; Behrendt et al., 2018; Canavan, Unwin, Kelly, & Connolly, 2008; Chaturvedi et al., 2001; Jeffcoate, 2005; Kennon et al., 2012; Moulik, Mtonga, & Gill, 2003; Spoden, Nimptsch, & Mansky, 2019) consistent methodology is rarely used (Narres et al., 2017; van Houtum & Lavery, 1997).

An attempt of standardisation of methodology was attempted by the Global Lower Extremity Amputation Study (GLEAS) group (Unwin & Group, 1995) but it was not widely adopted. GLEAS looked at all amputations but did ask for participants to specify if patients had a history of diabetes. It identified a large difference in amputation rate between populations, with the highest rates seen in native Americans and the lowest within the Spanish population. The association with diabetes also varied from between 25 to 90% of all amputations performed dependant on region. Standardisation was again attempted by the VASCUNET collaboration, but its methodology has not been widely disseminated (Behrendt et al., 2018). Most studies demonstrate decreasing incidence of major amputations, with the numbers of minor amputations increasing simultaneously within the diabetes and non diabetes populations. (W. A. Davis, Norman, Bruce, & Davis, 2006; Gregg et al., 2014; Kennon et al., 2012; PHE, 2019). Some demonstrate no change in rates (Buckley et al., 2012; McCaslin, Hafez, & Stansby, 2007; Trautner, Haastert, Spraul, Giani, & Berger, 2001; E. P. Vamos et al., 2010a) and some demonstrate an increase in rates, even within the same population (Eszter Panna Vamos, Bottle, Majeed, & Millett, 2010b). There are marked differences between the rate within developed and developing countries and between European countries with changes seen over time(International Diabetes Federation, 2019). The predominance of literature in the western world supports a reducing rate of major amputation with reduction noted in the USA and Australia (Kurowski et al., 2015; Lazzarini, O'Rourke, Russell, Derhy, & Kamp, 2015). Despite the percentage of people with diabetes undergoing amputation decreasing the prevalence of diabetes is increasing and with it the crude numbers of amputations.

The most recent paper produced by Public Health England (PHE) on the amputation rates in the diabetes population within England reported a reduction in the rates of major amputation but an increase in minor amputation rate. Between mid 2015 and 2018 there were 7,545 major amputations and 19,920 minor amputations performed, giving a directly age and ethnicity standardised rate of 8.2 and 21.4 amputations per 10 000 population-years respectively (PHE, 2019). In the majority of epidemiological studies, amputation rates are presented for total numbers of amputations, combining the rates of major and minor amputations or for major amputations alone. This confuses the trends presented as minor and major amputations are often performed for different indications; minor amputations can be seen as a curative treatment rather than an outcome of a disease process. The outcomes following both procedures are vastly different along with the populations they are performed in. There is also no standardised definition of major and minor amputation within the literature. This along with variance in the denominator definition, selection and standardisation measures used make analysis between papers and populations problematic.

Incidence and rates of amputation have been documented in other areas of the UK with papers from health bodies in England, and analysis of health data in Scotland and Ireland (Buckley et al., 2012; Kennon et al., 2012; PHE, 2019). There is variation in the rates between and within the individual countries. For example, the incidence rates vary in Scottish (Kennon et al., 2012) as well as English localities (Naseer Ahmad et al., 2014; PHE, 2019). Therefore, amputation rates for different areas of the UK are likely to show considerable variation and cannot provide an accurate estimation of the picture within Wales. This is confounded further by large variations in the amputation rates from within countries. Ahmed et al noted a large variance between the incidence rate of amputation between Northern (31.7 amputations/100,000 per year) and Southern England (23.1 amputations/100,000 per year)(Naseer Ahmad et al., 2014). There was as high as a 50% variation across regions which remained over time despite falling rates of amputation in England. This variance has been noted in other developed countries with an 8.6-fold variation in the incidence of major amputation between states noted in the USA (J. S Wrobel, Mayfield, & Reiber, 2001) along with a 2 fold variation between hospital districts in Finland (K

Winell, Venermo, Ikonen, & Sund, 2013b). There is also variance in rates of change over time between populations with and without diabetes and between genders. The variation in rate between health boards in England was greater within the male population and this inequality persisted despite major amputation rates decreasing over the study period. Major amputation rates were decreasing faster in the population with diabetes compared to that without, this was felt to be secondary to targeted policies (Naseer Ahmad et al., 2014) and different trends were demonstrated with minor amputations, with rates rising in non-diabetic men. Rates need to be explored thoroughly to highlight the nuances between groups to adequately target sparse funding to appropriate areas.

At present, no information on the current or historic amputation rates within the diabetes and non-diabetes populations have been published within Wales. Information is available through the national vascular registry, a database in which vascular procedures are self-reported by surgical teams (National Vascular Registry, 2018). The data is not correlated against hospital episode statistics (HES) data, only provides information on major amputation and there has been variance in the compliance rates between areas in Wales, giving only a partial picture. The only published data within Wales at present is a study exploring re-amputation recurrence in a population requiring prosthesis within one health board (Kanade et al., 2007). Forty six percent of patients with a single lower extremity amputation and diabetes underwent re-amputation. There was a 22% incidence of contra-lateral lower extremity amputation within 2 years in the population with diabetes. In comparison only 15% underwent re-amputation in patients who underwent amputation for a vascular aetiology alone.

Data is also available from NWIS, for crude major amputation rates based on HES data and is available on request. Data on diabetes status is based on data provided from the national diabetes audit from the year in which the amputations occurred which gives an estimated rate dependant on participation in the audit. Data provided is per diabetes population and there is not a way of identifying if amputations are secondary to diabetic foot disease or another

aetiology. The data is also not age or sex standardised making it impossible to determine if changes over time or between health boards are due to changes in the structure in health board demographic data. This makes comparison to the rest of the UK unreliable and although useful for crude trends, makes it difficult to make assertions on care from.

1.5.2.1 Cost

Foot lesions and amputation are associated with a substantial economic consequence (Boulton et al., 2005). Up to 20% of the expenditure on diabetes worldwide in spent on foot problems. The highest cost is generated from ulceration, with a large proportion of this due to the cost of inpatient care, social services and home care. This is particularly concerning as ulceration is a recurrent issue once it occurs. After healing, the re-ulceration rate at 1,3 and 5 years is 34%, 61% and 70% respectively (International Diabetes Federation, 2019). These costs then increase exponentially if patients go on to require amputation of which 82% are preceded by ulceration. The cost of ulceration and amputation in England between 2014-2015, as estimated by Kerr et al, was between £837 and £962 million (M. Kerr, Rayman, & Jeffcoate, 2014). This was almost 1% of the NHS budget for England, greater than the expenditure for three of the most common cancers combined. More than 90% of the expenditure was related to ulceration and 21 million was spent annually on post amputation care. The cost of the major amputation procedure alone was £2,477,252, £16,910,258 for minor amputations and £2,114,851 was spent on stump revisions.

There are also associated indirect costs caused by loss of productivity and the individual financial and physical costs to the patient and family. Indirect costs encompass sickness, work absence, disability status and the cost to the person, workplace and government. Indirect economic costs come from loss of the productive work force through permanent retirement, morbidity affecting working productivity and the loss of working age adults due to morbidity and mortality. Further to this are the intangible losses associated with amputation such a pain, anxiety, inconvenience and other factors which can reduce and negatively impact quality of life (QOL)(WHO, 2016)

1.5.2.2 Mortality

Morbidity and mortality data related to major lower limb amputations show exceptionally poor results. The estimated 5-year mortality for major amputation is as high as 80%, higher than most common cancers(Diabetes UK, 2015c). In people with diabetes in England, the median survival after amputation of any cause has been reported to be 20 months shorter than persons without diabetes (Scott et al., 2014). In hospital mortality for major amputation is reported to be as high as 8.3% (Ambler, Thomas-Jones, Edwards, & Twine, 2019). Even those people who develop foot ulcers that do not progress to amputation have an approximate twofold increased risk of death compared to the diabetic population without ulcer (Robbins et al., 2008). A high mortality rate is associated with major amputation and is to be expected as the population undergoing amputation are often frail, multi-morbid, and as a low predicted life expectancy can be used as an indication for major amputation by operating physicians when management is being considered (Thorud, Plemmons, Buckley, Shibuya, & Jupiter, 2016). As expected, there is variance in outcome by operation performed. The short- and long-term mortality for minor amputation is less than that seen for major amputation likely due to the nature and indications for the procedures and the populations the procedures are performed in.

As well as variance in amputation rate between geographic location, a variance in mortality following major amputation has been documented (Behrendt et al., 2018). As with amputation incidence, direct comparison of mortality rates following amputation can be difficult due to differences in population, amputation definitions and reporting. At present there has been no data published about amputation related mortality in the population with diabetes in Wales. With variability in mortality between populations previously reported, for future healthcare planning it is also important to investigate mortality within Wales.

1.5.3 The risk factors for amputation

Numerous factors have been identified that increase the risk for amputation. Whether patients will go onto amputation secondary to diabetic foot disease is conditional on factors related to the limb, person and population (K. M. Pickwell et al., 2013; Prompers et al., 2008) or on physical, psychological and societal factors. The three common risk factors for ulceration, neuropathy, PVD and infection also play a key role in amputation (Figure 1.4). They are responsible for structural foot deformities, poor blood supply, ulceration and the insensate foot (Edward J. Boyko, Seelig, & Ahroni, 2018). Beyond these limb related factors, there is a complex interaction between the environmental, lifestyle, clinical and genetic factors. The way that these interact within populations varies and as of yet, no model has been able to fully predict amputation risk in patients with diabetes.

The commonly accepted limb and clinical risk factors are neuropathy, callus, absent pulses, a history of previous ulceration and foot deformity, poor diabetic control as measured by HbA1c and ESRD in particular if dialysis is required (Paneni at al., 2013). In one of the most widely cited prospective studies examining amputation risk factors, the Seattle prospective study, identified limb and person level risk factors associated with amputation were a history of neuropathy, a low and high APBI, poor EGFR and poor vision. Interestingly the study found that amputation risk reduced after the age of 70 years, a finding that has not been confirmed in other studies, but it may have been that death was a competing risk, which was not accounted for. They also identified that increasing weight reduced the risk of amputation. Commonly accepted foot related factors include wound depth, severity and presence of infection. These increase risk of amputation in those patients presenting with a diabetic foot, whether that be with neuropathy, PVD, infection or a combination (D. G. Armstrong, Lavery, & Harkless, 1998; Oyibo et al., 2001). This is reflected in the findings of the national diabetic foot care audit with those with the biggest ulcers, the least likely to recover. This has led to the development of a number of wound/ulcer scoring systems such as the IWGDF classification system and the PEDIS classification to help clinicians identify those patients at greatest risk (Benjamin A Lipsky et al., 2016; K. Pickwell et al.,

2015). Person related factors include ESRD and the requirement for dialysis, high serum glucose, duration of diabetes and requirement for insulin treatment, men, smoking history, low BMI and ethnicity (E J Boyko et al., 1999; C. Lin, Liu, & Sun, 2020).

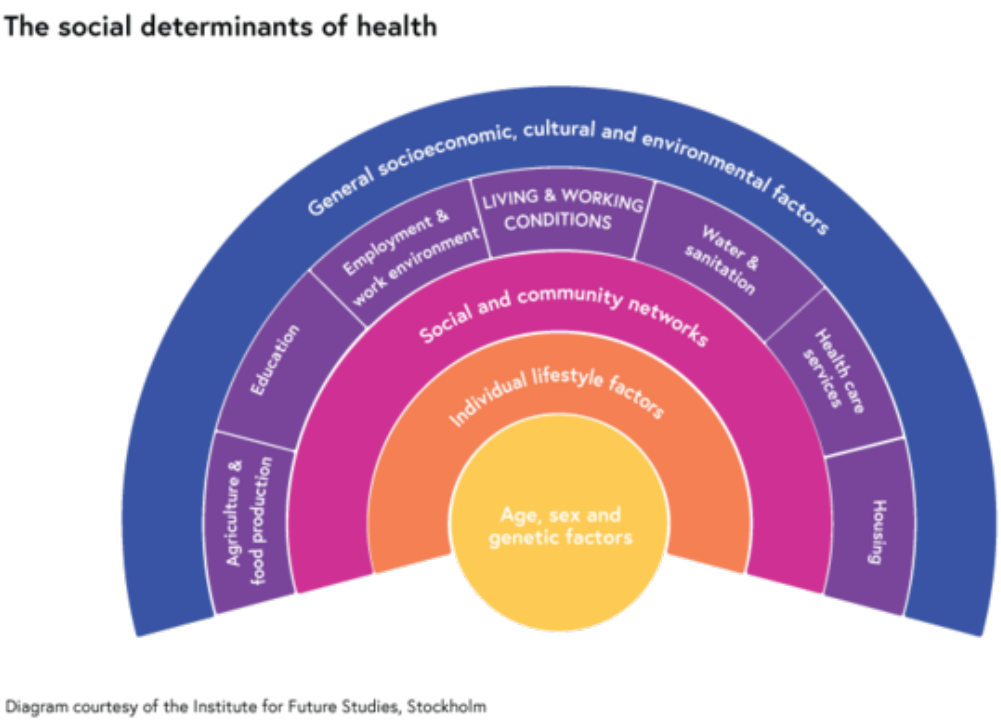
Many of these risk factors are modifiable and some are related to individual behaviour patterns, many of which vary between country and within socio-economic groups. In a recent study of hospital data, the International Variations in Amputation Practice: A VASCUNET Report, found that diabetes prevalence, age distribution, amputation risk factor prevalence and mortality rates were found to vary between countries (Behrendt et al., 2018). It is unsurprising then that geographic variance in amputation rates is seen. It is important then to view risk factors holistically and identify issues and their driving factors within individual populations.

Along with clinical risk factors, a number of psychological and socio-economic factors have been identified that contribute to amputation risk. Individual behaviour patterns have been shown to have an effect on amputation risk and are often present along a social gradient. Those from a lower socio-economic background are at an increased risk of trauma. Barefoot gait in India markedly increases the risk of amputation (International Diabetes Federation, 2019) and within the developed world persons from within a lower socio-economic group are more likely to have manual jobs increasing the risk of initial trauma and the inability to comply with treatments such as offloading due to the requirement to work (Costa, Tregunno, & Camargo-Plazas, 2020; Mrdjenovich, 2011). These risks are associated with education, peer support and environment (Lepäntalo et al., 2011).

There are many reasons for variance in outcome in health. Some variance is accepted, such as the change in health with age and some is unacceptable such as the variation in outcomes with socio-economic deprivation. These changes fall into the remit of health inequality and it is these areas that contribute to disease in a complex manner. If not addressed, they impact all aspects

of a person's health and wellbeing (Figure 1.6), along with having great economic costs. The Marmot review of health inequalities identified that inequality in illness costs the UK annually £5.5 billion in health care costs, £25 billion in welfare payments and taxes and £32 billion in losses due to productivity (Marmot, 2020). Socio-economic disparities exist in both overall disease prevalence and outcomes. There is inequality in access to healthcare and increased mortality and morbidity rates in a number of diseases including diabetes in less advantaged communities within the UK. It is important to understand and highlight these inequalities especially when associated with inequalities in outcome as they can be used to guide policy and planning. Although multiple factors play a role in amputation it is important that within the NHS access to healthcare and the 'postcode lottery' do not contribute to complications.

Figure 1.6 The Social Determinants of Health



Reducing inequities is a key driving factor for health care in Wales and forms a main priority within 'Our Healthy Future', the Strategic Framework for Public Health In Wales, following a report identifying a stalling in life expectancy and mortality improvements since 2011(Public Health Wales, 2020).The report highlighted the growing disparity in health outcomes between the least and most deprived groups within Wales. There is marked disparity in mortality, risk of disease and access to preventative services. Men from the most deprived quintile of Wales not only have a shorter lifespan, but also spend less of their life in good health (77%) compared to those living in the least deprived fifth (89%). The same is true for women (74% vs 86%) (Public Health Wales, 2016).

There is evidence that these inequalities can be addressed. A prime example in Wales in a population with the same underlying pathophysiology to most undergoing amputation, is access to cardiovascular revascularisation services. After a service redesign in the provision of revascularisation procedures the significant disparity in revascularisation rates between the most and least deprived quintile in Wales was ameliorated when adjusting for other confounding factors. This was achieved through increasing the capacity of services such as primary coronary interventions, as with those requiring revascularisation for amputation, those in the most deprived quintile had the worst access despite the greatest need (Evans, van Woerden, Davies, & Fone, 2016). Coronary artery disease has the same underlying disease process i.e atherosclerosis, risk factors and treatment strategies as PVD and most patients with PVD and diabetic foot disease die of CVD (Malyar et al., 2016; Mundell et al., 2018).

There are clear associations between social deprivation, diabetes, and ulcer formation. In a study of a UK based population with diabetes, those in the most deprived quintile had a 1.7% increased risk of ulcer formation (95% CI:1.2-2.3%) (Leese, Feng, Leese, Dibben, & Emslie-Smith, 2013). The association between deprivation and amputation is less clear in the literature but most studies performed to date have had issues with being underpowered. In the same UK based study, only a history of previous foot ulcer, impaired sensation when assessed with monofilament and

absent pulses predicted amputation. There was a trend was towards an association between deprivation and amputation but the number of amputations performed were much smaller than the number of ulcer formation. These findings were mirrored in a nationwide study within Finland. Low socio-economic position was again associated with an increased risk of incident major amputation and further to this, an increased rate of re-amputation within the 2-years following their initial procedure (Venermo et al., 2013). The study did not control for other potentially confounding risk factors such as CVD and ESRD. Ferguson et al did find an association with social deprivation and amputation risk in a very large Canadian population-based study of 60,6494 patients with universal health care(Ferguson, Nightingale, Pathak, & Jayatunga, 2010); low socioeconomic status greatly increased the risk of amputation. However, the study defined socioeconomic status based on neighbourhood level income groups only (Amin et al., 2014). The risk associated with socio-economic deprivation was greater in men and it was postulated that this was due to a financial limitation to taking an absence from work for adequate treatment, poor health literacy and a compromised ability to advocate for their own health (Altenburg et al., 2011; Oladele & Barnett, 2006; Pinkhasov et al., 2010). The variance in the risk of foot ulceration and amputation with social gradient have been attributed to variance in and ability to perform self-care, access to nutrition and appropriate footwear and health-risk behaviours (Margolis, Hoffstad, & Weibe, 2014; Petherick, Cullum, & Pickett, 2013; Venermo et al., 2013). Only a few studies separated type of amputation in their analysis. In the study of the Finnish population, although underpowered there was variance in the number of minor and major amputations performed by income. For the whole population minor amputation rates increased as major amputation levels decreased but there was a gradient by income and by education with those in the highest income groups and education groups having the largest major to minor amputation ratio (Venermo et al., 2013). An important factor, as prevention of amputation relies on appropriate preventative steps at a holistic level and in an ambulatory setting. Minor amputations are often used as a preventative treatment and there is evidence to suggest that patients from a lower socio-economic class are less likely to get preventative treatment, whether that is due to more severe disease at presentations, clinical decision making or access to care (Bernheim, Ross, Krumholz, & Bradley, 2008; Gornick et al., 1996). There may be missed

opportunities for patient education, risk factor modification and early detection and management for persons of a lower socioeconomic status. There is also a chance that the association between deprivation and amputation could be secondary to reverse causation with those undergoing amputation at greater risk of job loss and therefore progress into a lower socio-economic category.

Societal factors can affect access to care, education and medication. People in lower socioeconomic area less likely to be provided a good standard of education and engage in health care behaviours. Lower socio-economic status is associated with excess alcohol use, disproportional smoking rates and other adverse health behaviours, this is especially true in men (Wang & Geng, 2019). Smoking is closely tied to socioeconomic deprivation within Wales with smoking attributable hospital admissions and mortality twice as high in those living in the most deprived areas compared to those in the least deprived areas of Wales. This has not changed in the last 10 years and in some areas has even increased despite the general decrease in the smoking prevalence in Wales (Public Health Wales, 2017). In the VASCUNET study the countries with the highest major amputation rates had the greatest quantity of current smokers and the countries with the lowest rates had the highest population of never smokers(Behrendt et al., 2018). In a large meta-analysis looking at clinical and behavioural risk factors, smoking and male gender were identified as the individual significant risk factors for amputation (Shin, Roh, Lee, & Yang, 2017). The disparity in amputation rates in men is in part explained by physiological factors associated with neuropathy as described previously. Men are on average taller and more likely to experience neuropathy. It has also been demonstrated that men are less likely to seek timely care, use primary care and engage in preventative measures (Malcher, 2011; Witty, White, Bagnall, & South, 2011). They also have a higher chance of occupational injury.

At present as most studies of socioeconomic status have been epidemiological focusing mainly on population and procedure rates, they have not taken into account potential psycho-social confounding factors such as education level as these are not very well documented in health data

and very few studies have been performed exploring socio-economic status along with limb related factors as socio-economic status is not well documented in clinical notes. Most studies are either limb and person level, or person level and socio-economic and it difficult to address this issue in epidemiological studies alone. Different study types can be utilised to further explore high risk groups. The effect of socioeconomic deprivation varies between countries and this has not yet been explored in Wales. Nor have prevalence rates been quantified by socioeconomic deprivation in Wales.

Ethnicity may also play a role in amputation outcomes although the relationship is complex and its effect varies by location. There is a known variance in the prevalence of diabetes in different ethnic groups within the UK. Rates are particularly high in Black Caribbean men and women, South Asian men and Pakistani women(International Diabetes Federation, 2019). Variation in rate of amputation with ethnicity is more complex and there is clear differences dependant on location. In the UK and across Europe, there is a reduced incidence of diabetes related foot ulceration and amputation in Asian and Afro-Caribbean populations despite a higher prevalence of diabetes (Leggetter, Chaturvedi, Fuller, & Edmonds, 2002). There is poor understanding of these disparities but theories include variance in height, smoking status and skin microvascularization (Abbott et al., 2010; Robinson et al., 2015). Within USA the risk of amputation in ethnic minority populations is markedly increased despite the rate of ulceration being similar. These differences are felt to be due to disparities in access to health care and how these interact with social deprivation in the different countries (ADA, 2018; Chaturvedi et al., 2001; Leggetter et al., 2002). Despite access to free healthcare there is still a higher incidence of stroke, HTN and PVD in the black population within the UK (Vitalis, Lip, Kay, Vohra, & Shantsila, 2017). The association between ethnicity and neuropathy suggests a reduced risk in ethnic minority groups within the UK but this has been more extensively explored in south Asian populations and doesn't wholly explain the variance in amputation risk (Chaturvedi et al., 2002; Tahrani, Altaf, Piya, & Barnett, 2017). The reasons for the differences between geographical regions and the extent to which health care systems are responsible is not clear (Chaturvedi et al., 2001). Within Wales there is very little ethnic diversity; 94% of the population identify as

White British. There is greater variance in some health boards such as Cardiff and Swansea, but reports have shown there is little difference in outcomes in health between ethnic groups in Wales. The most recent ethnicity and health in Wales report, based on the 2011 census, identified that persons within the mixed multiple ethnic group classification reported the highest levels of bad or very bad general health, but the differences between groups were not significant with only a maximum 3% difference between ethnic groups for reports of limiting illness and bad/very bad general health (Public Health Wales Observatory, 2015).

Geographic variation in amputation rates may be in part explained by practitioner variation (Margolis et al., 2014). Some of the variance in the incidence of amputation in England has been partially attributed to the surgeons concerned. In a small case control study, some correlation was identified between training and a professionals belief on management and complication rates (Connelly, Airey, & Chell, 2001). In some regions of England, a high rate of major and minor amputation in the diabetes and non-diabetes populations has been identified, even when controlling for population differences. This is suggestive that there is some geographical variance in readiness to operate (Holman et al., 2012). This has also been shown to transfer to rates of amputations in the population without diabetes, suggesting that variance between health boards is in part due to care pathways (P. W Moxey et al., 2010b) . In a 2015 PHE report looking at healthcare inequalities the relative risk of major lower limb amputation in the population with diabetes compared to those without diabetes ranged from 0.0 to 17.6-fold. When comparing the central range of these Clinical commissioning groups (CCGs) the variation between them was 3.9-fold. The data was not standardised for ethnicity and one reason purported for the variation observed was differences in the ethnic composition of local populations because the pattern of diabetes complications varies by ethnic group: people with diabetes from South Asian and Black ethnic groups are significantly less likely to experience diabetic foot disease and therefore have a lower risk of lower limb amputation than their peers from White ethnic groups. It was felt though that ethnicity was unlikely to account for all the variation, and some of the variation may be due to differences in the organisation of care for people with diabetes. This also did not take into account the areas where general amputation rates are high, as it has been demonstrated

that in areas in which diabetes related amputations increase so are non-diabetes related amputations (IDF, 2015) Again, this can be difficult to assess at an epidemiological level and often requires exploration of cases within a centre. Once such methodology which can determine and question the ethos within an area is root cause analysis (RCA).

1.5.4 The prevention of amputation

Prevention of amputation is a priority as even minor amputation is the end outcome of a long disease process. This is especially true when It has been postulated that as many as 80% of amputations related to diabetes can be prevented with adequate care. Interventions to prevent amputation are multifactorial and complex but methods to prevent foot ulceration and amputation have been shown to be cost effective or even cost saving (Ragnarson Tennvall & Apelqvist, 2004). This is before considering the cost on quality and length of life for the patient. Interventions are multitude and require many specialties and all levels of care settings. Within the western health care system there is strong evidence that In North America and Western Europe that preventative foot care and education, close monitoring and a MDT approach to treatment of foot disease can lead to significant reductions in ulceration and ultimately amputation (International Working Group on the diabetic foot, 2019; Larsson, Apelqvist, Agardh, & Stenström, 1995; R. B. Paisey et al., 2018a).

As with any disease process, in the UK, the entry point of care should be primary care. There are a number of guidelines such as the Quality and Outcomes Framework (QOF), which support annual monitoring within the primary care setting for diabetes patients. Early identification of common risk factors allows for preventative and curative services to be provided. As primary care encompasses care of the whole patient, it is best placed to address the person holistically. Other risk factors should be addressed such as PVD, neuropathy, HTN, hypercholesteremia, obesity, smoking and foot risk behaviours through foot care education. Patients will progress from primary care to secondary via podiatry, vascular, endocrinology or orthopaedics as well as through retinopathy screening. The pathways between primary and secondary care need to be

clear and readily available. The way in which this is approached within the UK is through grading of the diabetic foot.

NICE guidelines and Diabetes UK recommend for persons to be assigned a foot risk as part of the standard of care. Persons with diabetes should be offered at least an annual review of their diabetes and part of this assessment must involve review of the feet. Persons are assigned a foot risk category (Table 1.2). This risk then determines the requirement for frequency of rescreening and clarifies the requirements for referral to further services. NICE recommends referral to a community foot protection service for those who are moderate or high risk and to acute services with referral to the foot care MDT if the person has a limb-threatening or life-threatening diabetic foot problem. It is also a key requirement that a person is aware of their own foot risk and are offered education on how to perform basic foot care and the importance of it.

Table 1.2 Foot risk categories as described in NICE diabetic foot care guidelines

Risk category	Findings
Low	Normal foot
	Callus alone
Moderate	One of: Deformity
	Neuropathy
	Non-critical PVD
High	History of ulceration or amputation
	On dialysis
	Neuropathy and non- critical PVD
	Neuropathy with callus or deformity
	Noncritical PVD with callus or deformity
Active foot problem	Ulceration
	Spreading infection
	CLI
	Gangrene
	Signs or suspicion of Charcot arthropathy

PVD: Peripheral vascular disease; CLI: Critical Limb Ischaemia

1.5.4.1 Education

Education in meticulous foot care and glycaemic control is a cornerstone of treatment of the diabetic foot according to NICE. Education should include foot hygiene; footwear use and the importance of prompt evaluation of any new foot lesion. NICE and Diabetes UK both view foot care education as integral in the management of diabetic foot disease. Diabetes UK in its recent 'Putting feet first' position statement highlighted the importance of persons with diabetes being involved in their own care with an emphasis on knowledge of foot care behaviours, risk of complications and awareness of what their health service should provide (Diabetes UK, 2015c). Based on clinical wisdom, common practices and international consensus, the risk of foot ulceration and ultimately amputation is felt to be reduced by education stressing the importance of routine preventative care, appropriate shoes, smoking cessation, lipid control and adequate glycaemic control. Despite this, large population-based studies have highlighted that a quarter of diabetic persons may never examine their feet (Johnston et al., 2006; Safford, Russell, Suh, Roman, & Pogach, 2005). This rate has been shown to vary between populations, globally, and between age groups (Chen et al., 2018).

Despite education becoming a cornerstone of non-medical intervention, the literature on its effectiveness was identified as inconclusive by NICE due to the low volume and poor quality of studies (NICE, 2016). Although recommended, specific foot care education isn't mandated or monitored within the UK. NICE recommend further exploration of the effect of education on outcomes of the diabetic foot as the literature available has often used unvalidated tools for measuring knowledge and behaviour and short follow up periods that allow only for identification of short term changes in knowledge or behaviour, not changes in medical outcomes such as ulceration or amputation (NICE, 2016).

Education programmes have proven successful in other aspects of diabetes management. Structured education programmes are the cornerstone of glycaemic control. In a systematic review of self-management education programmes Chrvala et al found that 61.9% of educational

interventions achieved improvements in HbA1c when compared to the standard of care in the period following the intervention(Chrvala, Sherr, & Lipman, 2016). There is evidence to suggest that this benefit is not long lasting and a push towards continuous education has been adopted by NICE and within Wales. Along with participation in the national diabetes audit, the 'Together for Health: A Diabetes Delivery Plan (2013)' requires health boards in Wales to provide "NICE-compliant structured education programmes"(NHS Wales, 2016). This is mainly focused on glycaemic control and compliance with medication as outlined in NICE guides and less attention is placed on foot care. At present there is not standardised programme for foot care education and quality of teaching and outcomes have not been audited. A 'Making Every Contact Count' NICE approved scheme has been introduced across health boards in Wales. This is an approach to behaviour and lifestyle change in which opportunistic advice is given about diabetes and health management in the clinical setting (Bennett, 2015; Public Health Wales, 2016) but this scheme does not address foot care and there is no reported outcomes beyond proposed benefits as of yet (Johnson et al., 2018).- In a large meta-analysis, intensive glucose management has been shown to reduce this risk of amputation by as much as 35% in persons with T2DM (Hasan et al., 2016) and education played a key role in this.

1.5.4.2 Multidisciplinary team working

The other cornerstone of management of the diabetic foot is the use of MDT. A foot care MDT is suggested as a basic requirement for quality care of the diabetes foot by both NICE and Diabetes UK (NICE, 2016). NICE recommend that services should provide an MDT that incorporates the skills of a diabetes physician and diabetes specialist nursing, vascular and orthopaedic surgeons, interventional radiology, microbiology, podiatry, orthotics with the ability to provide casting. There should also be access to other services such as rehabilitation, psychological and nutritional support as required.

The diabetic foot audit has highlighted that healing potential of an ulcer is associated with the length of the ulcers presence at presentation to a specialist centre. Even if other healthcare

practitioners have been utilised, the benefit of an MDT is clear. MDTs streamline pathways and clarify services allowing a smooth transition for the patient between services and towards the correct treatment. Collaborative working can minimise duplication and enhance the streamlining of services and patient experiences (P. M. Williams, 2001). As discussed above, individual clinician's decision making may affect amputation rates. MDT may mitigate these decisions through the effect of a variety of clinicians, that may have worked in different regions, working as a moderating influence in the interdisciplinary discussion. Treatment plans decided within a MDT for high risk patients have been shown to reduce major amputation rates (Forsythe, Brownrigg, & Hinchliffe, 2015).

The use of specialised foot care clinics and MDT has been widely accepted across the world. In most countries there has been a reduction in amputation rates with implementation of public health and MDT (Alvarsson, Sandgren, Wendel, Alvarsson, & Brismar, 2012; Canavan et al., 2008) with the importance of MDT and specialised clinics promoted as early as the 1980s (Edmonds et al., 1986). Most studies demonstrate decreasing incidence of major amputations, with the numbers of minor amputations (W. A. Davis et al., 2006; Gregg et al., 2014; Kennon et al., 2012; PHE, 2019) increasing simultaneously within the diabetes and non-diabetes populations. Specialised foot care clinics have been shown to reduce amputation rates in France, Netherlands, the UK and Italy. In Northern Europe, an increase in the number of specialist podiatry services within hospitals from 32-72% has been association with a reduction in major amputations within the population with diabetes from 5.5 to 3.65 per 10 000 persons, despite rising amputation rates (P. W. Moxey et al., 2010a; van Houtum, Rauwerda, Ruwaard, Schaper, & Bakker, 2004). In the Fremantle study, a large population-based study in Australia comparing the amputation rates between 1993-1996 and 2008-201,1 there was a stark 72% reduction in lower extremity amputation. This was attributed to the introduction of primary care foot health programmes (W. A. Davis et al., 2006). In other countries there have been reductions in amputation rates secondary to MDT clinics and streamlining of care pathways between care levels within the developed world (International Diabetes Federation, 2019).

Changes in practice within the UK have been shown to reduce amputation risk (Krishnan, Nash, Baker, Fowler, & Rayman, 2008; McCabe, Stevenson, & Dolan, 1998). The use of RCA to identify areas for service improvement and implementation of these changes have produced a reduction in amputation rates in a number of regions, saving potentially thousands of limbs (N. Ahmad et al., 2019; R. B. Paisey et al., 2018a). Units with a formal MDT in place have been shown to have favourable amputation rates (Holstein, Ellitsgaard, Bornefeldt Olsen, & Ellitsgaard, 2000; Krishnan et al., 2008; Schofield, Yu, Jain, & Leese, 2009). This was demonstrated definitively in the South West of England following a peer review of services introduction following an RCA of major amputations(R. B. Paisey et al., 2018a). A marked reduction in amputation rates were demonstrated in all CCGs that implemented the recommended services, with no change in amputation rate seen in those that did not implement an MDT. For change to be monitored, prospective review is required and this has been shown to improve outcomes in other medical fields utilising RCA (Perkins, Levy, Duncan, & Carithers, 2005a) as well as for major amputation (R. B. Paisey et al., 2018a) and an MDT would provide an opportunity to develop a prospective review of services as all patients are managed within the same pathway

1.6 Objectives and aims

The increasing incidence of amputation secondary to diabetic foot disease presents an ever-growing burden on the NHS and UK economy. This had led to a push towards a change in outcomes within Wales, with greater importance being placed on preventative diabetes foot care. This has been demonstrated through the introduction of the Diabetic Foot Network Wales. To assess whether interventions proposed through the Diabetic Foot Network are successful, there is a need for accurate information on current amputation rates and mortality within Wales. This data is currently unavailable within the literature and there is a general sparsity of information about the population of patients undergoing amputation secondary to diabetic foot disease in Wales.

Outcomes of diabetic foot disease are affected by risk factors at the person, healthcare system and population level along with the care provided. As well as understanding the current amputation burden, there is a need for a review of services to identify variance from the gold standards, including in education provided. Furthermore, an understanding of the risk factor profile and current knowledge of protective behaviours in the population would help in the development of preventative programmes.

The objectives of this thesis were firstly to examine the root cause and risk factors for diabetes related amputations within the Swansea locality and to understand patient's views, behaviour and expectations for foot care. Subsequently, further objectives were to examine the Wales incidence and risk factors for amputation in people with and without diabetes. The thesis therefore examines diabetes related amputation at an individual, a locality and at a national perspective. The specific aims of the thesis are:-

1. To perform a root cause analysis to identify factors contributing to major lower limb amputations in persons with diabetes within the Swansea locality.

2. To examine the social and clinical risk factors contributing to the risk of amputation in persons with diabetes referred to Secondary care services in the Swansea locality.

3. To examine the current knowledge, behaviour and expectations of foot care of persons with diabetes in the Swansea locality

4. To utilise the SAIL database to examine the incidence of lower limb amputation in people with and without diabetes in Wales between 2008-2018.

5. To utilise a Wales population-based approach to examine mortality following amputation in people with and without diabetes using the SAIL database.

CHAPTER 2

METHODOLOGY

The detailed methods used for each aim are described within the individual chapters. These can be found as follows:-

Aim 1: Methods described in chapter three, section 3.3

Aim 2: Methods described in chapter four, section 4.3

Aim 3: Methods described in chapter five, section 5.3

Aim 4: Methods described in chapter six, section 6.3

Aim 5: Methods described in chapter seven, section 7.3

2.1 Amputation description

Through the thesis amputations were classified as major if they were through ankle and above and minor if below, as per vascular guidelines (National Vascular Registry, 2018).

2.2 Statistical analysis

Throughout the thesis the normality of data was assessed using the Shapiro-Wilk test (Samanta & Schwarz, 1988). Continuous data with a normal distribution are presented with the mean and range. Continuous data without normal distribution are presented with the median and range. For all tests, statistical significance was set at $p < 0.05$. Detailed statistical analysis is provided within each chapter.

2.3 Health Board definitions

In April 2019 the Welsh government enacted a proposal moving the boundaries of the Bridgend, Cwm Taf University Health Board and Abertawe Bro Morgannwg University Health Boards. The health board names were changed to reflect the names the new boundary arrangements to Cwm Taf Morgannwg University Local Health Board and Swansea Bay University Local Health Board (Welsh Statutory Instruments, 2019). As research in this thesis occurred prior to this change, boundaries and names of health boards used will reflect the arrangements prior to 2019.

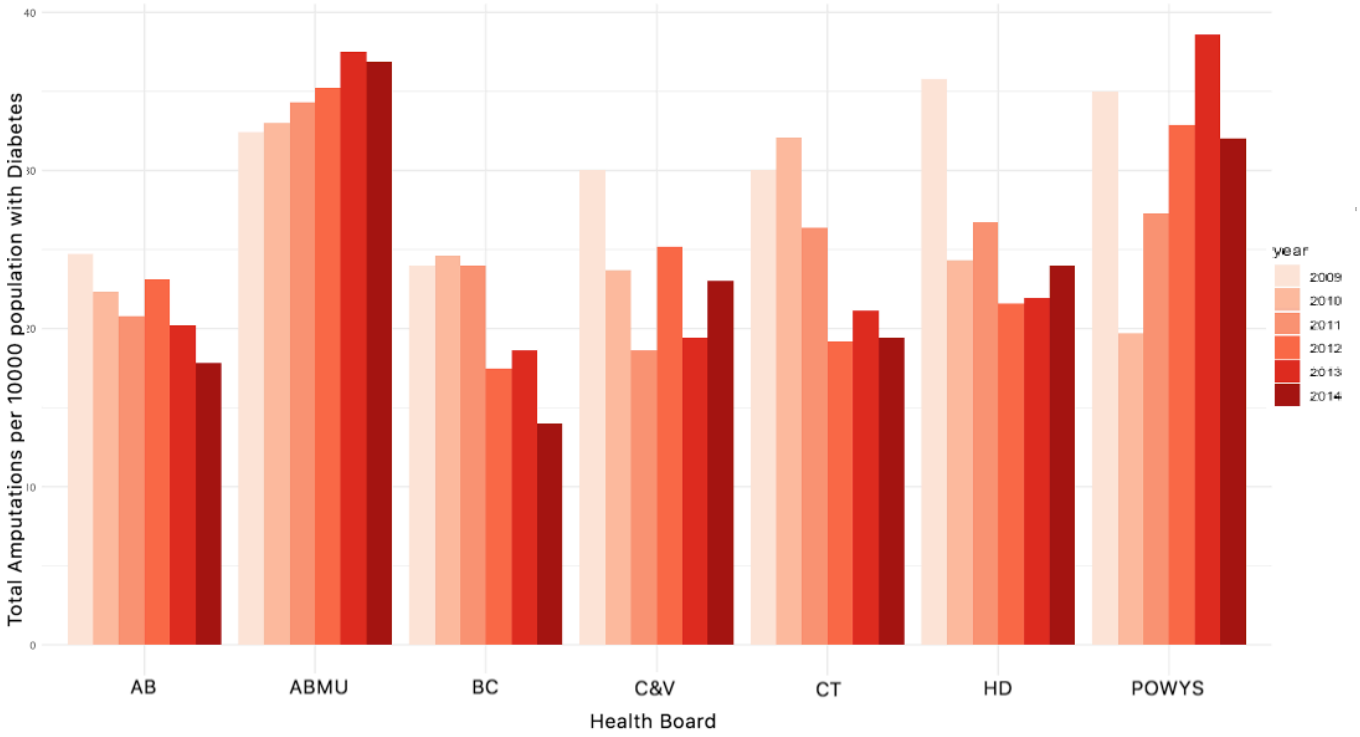
CHAPTER THREE

A root cause analysis to identify factors contributing to major lower limb amputations in persons with diabetes within the Swansea locality

3.1 Introduction

National data show up to a fourfold variance in the amputation rate throughout the UK (Holman et al., 2012). This is particularly evident within the Swansea locality (NWIS, 2017). The 2016 NWIS figures demonstrated that Abertawe Bro Morgannwg University Health Board (ABMU) had the highest rate of diabetes-related amputations within Wales (Figure 3.1 (NWIS, 2016)). This had been the case for the previous 6 years with amputation rates increasing year on year despite no difference in the number of new cases of diabetes compared to other health boards (Figure 1.1 (NWIS, 2016)).

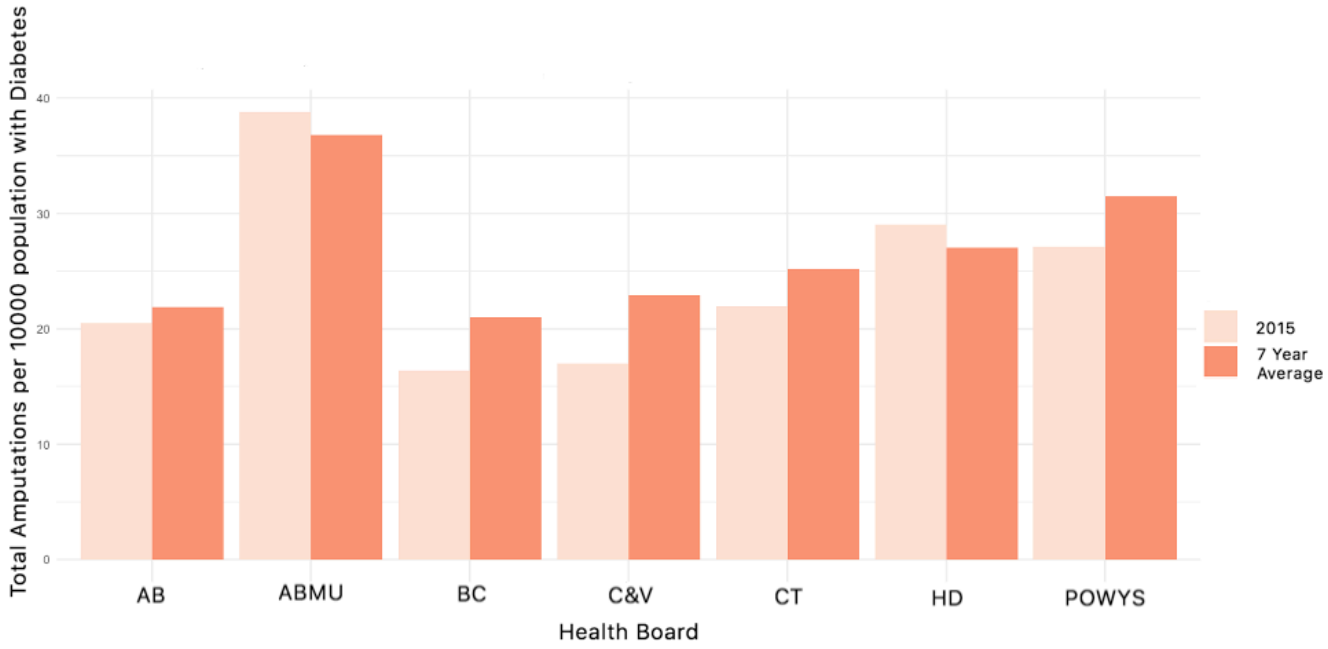
Figure 3.1. Total Amputations per 10 000 Diabetes Population across Welsh Health Boards between 2009 and 2014 as calculated by NWIS in 2016



AB: Aneurin Bevan; ABM: Abertawe Bro Morgannwg; BC: Betsi Cadwaladr; C&V: Cardiff & Vale; CT: Cwm Taff; HD: Hywel Dda.(NWIS, 2017) http://www.infoandstats.wales.nhs.uk/page.cfm?orgid=869&pid=41010&subjectlist=Principal+Procedure+%284+character+detail%29+by+LHB+of+Residence&patientcoverlist=Welsh+Residents&period=0&keyword=&action=Search (accessed 04/08/2017)

As discussed, NICE and Diabetes UK suggest that up to 80% of diabetes-related amputations can be prevented (M. Kerr et al., 2014) with adequate intervention. Apart from Hywel Dda Health Board (HD), ABMU is the only health board not to be achieving rate reduction. This is demonstrated when comparing the seven-year average amputation rate per 10 000 diabetes population within each health board to the 2015 rate. (Figure 3.3 (NWIS), 2016). If the rate was reducing, it is expected that the 2015 rate would be lower than the average. This is true in all health boards apart from ABMU and HD.

Figure 3.2. Seven-year average amputation rate versus the 2015 amputation rate per 10 000 Diabetes Population with diabetes across all Welsh Health Boards



AB: Aneurin Bevan; ABM: Abertawe Bro Morgannwg; BC: Betsi Cadwaladr; C&V: Cardiff & Vale; CT: Cwm Taff; HD: Hywel Dda (NWIS, 2017)
http://www.infoandstats.wales.nhs.uk/page.cfm?orgid=869&pid=41010&subjectlist=Principal+Procedure+%284+character+detail%29+by+LHB+of+Residence&patientcoverlist=Welsh+Residents&period=0&keyword=&action=Search (accessed 04/08/2017)

Although the available data does not assess for differences between population demographics or amputation type, it is suggestive that rates are higher within the ABMU Health Board. At present the reasons for the variance in health board outcome is not understood. This does not appear to be due to a higher incidence of diabetes and it is unclear at present what factors are responsible for driving this variance. A decision was made to performed a RCA as a first step in a long-term project to identify and improve outcomes of diabetic foot care within ABMU through the investigation of causative factors (Bagian et al., 2001).

Each health board has responsibility for the safety of the patients they are treating. The NHS defines patient safety as the avoidance of unintended or unexpected harm to people during the provision of health care, this includes avoiding preventable outcomes (NHS Improvement, 2019). Health boards are advised to record incidents relating to patient safety so learning can take place to reduce the risk of similar incidents occurring again. An important aspect of patient safety is the investigation of these incidents to identify and act on modifiable factors, reducing the likelihood of these events being repeated. It may be unrealistic to prevent all incidents (Hollnagel, 2004), however, it is recommended that organisations learn from deviations from expected care (Reason, 2008). A number of different frameworks have been created to analyse incidents (Hollnagel, 2004; Leveson, 2004; Salmon et al., 2011). Incident analysis methods act to guide an investigation and its analysts in the understanding of an incident, in the generation of recommendations and help to reduce bias. By using a systematic approach, the frameworks aim to reduce bias in analysis, avoid misinterpretation of data and help clinicians produce high quality reports with actionable recommendations. One such model often used within healthcare is RCA.

RCA is a process that facilitates the identification of the primary cause or causes of a problem, with the aim to determine the actions required to eliminate them (PSNet, 2019). A root cause is a condition that could have reasonably contributed to an adverse outcome (Perkins, Levy, Duncan, & Carithers, 2005b). The approach utilises a number of different strategies that assist isolation of the most fundamental cause of a problem. RCA has long been used in the airline and

engineering industry as a preventative strategy, used to retrospectively assess events to prevent error recurrence (P. M. Williams, 2001). It is a process which aims to identify the causative factors that contribute to an issue, so they can be addressed, rather than treating problems symptomatically as they arise. Over the last 25 years RCA has been adopted within the medical field to investigate adverse incidents; used at hospital, health board and governmental levels, as it allows focus on system causes rather than attributing blame (P. M. Williams, 2001).

The process normally comprises of five stages: determine the problem to be addressed; gather data for the analysis; identify the root cause or causes; take actions to eliminate the problem; and verify the results (National Patient Safety Agency, 2013). Unlike in the aeronautical and engineering industries, it is often difficult to eliminate the problem and verify results within the space of a review, as most problems involve multiple systems and observable impact takes time to emerge after changes have been implemented. RCA has been used successful in other health boards as a stepping-stone to redesign services and has been shown to be beneficial in reducing diabetes- related amputation rates over a 10-year period (R. B. Paisey et al., 2018a) if recommendations are followed. It is a tool recommended by Diabetes UK for services to reduce their diabetes-related amputation rates and who provide a framework to follow (Diabetes UK, 2017) along with evidence of previous successes (Diabetes UK, 2015a).

3.2 Aims and objectives

3.2.1 Objective

To identify the root causes of all major lower limb amputations performed in patients with diabetes between 2015-2016 within ABMU Health Board.

To use the information identified relating to modifiable factors to create recommendations to reduce the rate of future amputations.

The specific aims of this chapter are:-

(i) To establish the facts of each major amputation between 2015-2016 i.e. what happened, to whom, when, where, how and why.

(ii) To establish whether deviations from patient safety occurred in the care or treatment pathway.

(iii) To identify root causes for any deviations.

(iv) To establish how recurrence of deviations may be reduced or eliminated.

(v) To formulate recommendations and an action plan.

(vi) To provide a report and record of the investigation process and outcome; communicate these findings with the local health board.

3.2.2 Key questions/issues to be addressed

What is the cause of the variance in amputation rates in ABMU compared to the rest of Wales?

Could changes in our current care pathway be implemented to reduce the amputation rates?

3.3 Methods

3.3.1 Ethical approval & consent

The root cause analysis was deemed a service quality improvement project therefore no ethical approval was required to undertake the review (Appendix I). With approval from the Clinical Director for Primary Care, agreement was made to liaise with each patient's general practitioner (GP) to identify the process in primary care. In February 2017, letters were sent out by the orthopaedic clinical team to living patients to request consent for access to GP records. Deceased patients were presumed to have given consent (Appendix II). If consent was granted or presumed, the respective GP's were contacted. Patients who had not responded were contacted by phone and if consent was granted a letter was then sent to their GP.

3.3.2 Sample

All patients who underwent a major amputation secondary to diabetes-related foot disease between January 1st 2015 to December 31st 2015 within ABMU. All patients included were over the age of 18 years and had a diagnosis of either T1DM or T2DM on any treatment regime. Patients were identified post-operatively using NHS Wales Informatics Service (NWIS) data accessed by the health board IT service. Physical and electronic primary and secondary care notes were examined to confirm the occurrence of a major amputation and diagnosis of diabetes. Patients who had undergone minor amputations, were aged of 18 years or below, had undergone an amputation secondary to malignancy/trauma or had a revision of major amputation alone were excluded.

3.3.3 Study Design

3.3.3.1 Data collection

This was a retrospective, multi-incident, record review study of all major lower limb amputations occurring in people with diabetes between January 1st 2015 and 31st December 2015 in Morriston

Hospital, Swansea. Morriston hospital, a 700 bedded hospital, is one of the major vascular surgery hubs for the South Wales region and offers a tertiary care orthopaedic service.

NWIS data identified 89 cases of major lower limb amputation within the time period. Patient details were cross-checked by the orthopaedic clerical team, registrar and orthopaedic surgeon with electronic theatre record systems to clarify the indication and type of procedure. The theatre record system records the procedure date, time of procedure start and finish, details of the operating team and procedure details. These are recorded at the time of procedure by the theatre staff and surgical team and have to be available in the patient notes before the patient leaves the post-operative recovery area.

Of the initial 89 cases, 10 were excluded as they did not meet criteria for a major lower limb amputation. Five were minor amputations (4 re-amputation of foot at a higher level and 1 toe amputation) and 5 were repeat procedures within the time period (2 stump revisions, 3 conversions of BKA to AKA). Of the remaining major amputations, 3 were bilateral cases, leaving 79 major lower limb amputations that had occurred in 76 patients. Once identified, the secondary care clinical notes were requested.

Additional funding was sought and granted to the orthopaedic team for the work in accessing notes from medical records. In addition, secondary care ABMU podiatry notes were accessed. As discussed above, GP records were accessed after consent was obtained from patients. If consent was granted via return letter or presumed, the respective GP's were sent a letter of explanation and a proforma they were required to complete to establish the process in the primary care setting (Appendix II) and further primary care records were accessed through the Welsh Clinical Portal (WCP) in September 2017.

3.3.3.2 Data input

Using the paper and electronic notes, data on the amputation admission and any information available on the events leading to amputation, were entered into templates by clinical staff. This occurred over a one-week period in May 2017. The template was created using the Diabetes UK resource for RCA of major amputation and adapted for local use to capture pertinent data (Diabetes UK, 2017). It comprised of a Front / Podiatry / Chronology / Secondary Care and Summary Sheet (Appendix II). Data were gathered into individual patient packs and a timeline of events was mapped for each patient. Variance in care and factors associated with amputation risk were identified. Data were included from the first presentation with foot disease to the point of amputation (Table 3.1). The admission leading up to amputation was reviewed, in addition to preceding primary care, secondary care and podiatry data.

Table 3.1. Demographic and clinical information collected in RCA

Demographic Data	Clinical Data	Imaging
Date of Amputation	BMI	Foot and ankle x-ray
Gender	HbA1c	Angiogram
Smoking status	WCC	MRI
Hx foot disease	CRP	ABPI
Hx Amputation	Haemoglobin	
Medication		
Co-morbidities		
Duration of diabetes		

Hx: History; BMI: Body Mass Index; HbA1c: haemoglobin A1c; WCC: White Cell Count; CRP: C-reactive Protein; MRI: Magnetic resonance imaging; ABPI: Ankle brachial pressure index. Clinical data and imaging were collection from the amputation admission

The last day of the data entry week was dedicated to summarising the combined sources of data, allowing the combined clinical team to assess the cases. Contributory factors were identified in whole team discussions, assisted by and allocated into the National Patient Safety Agency (NPSA) Contributory Factors Classification Framework (Appendix II) (NPSA, 2009). It was not possible to use all the NPSA classes and contributory factors within the framework as data such as staff and

patients' views were not attainable within the scope of this RCA. Data were not available in the notes and funding was not available for interviews. The form was, therefore, adapted for the review, removing the factors that were not attainable (Appendix II). After the initial process week, further data for each of the events were required as all notes had not been retrieved.

Further secondary and primary care notes were retrieved, and after data input, part of the initial review team met again to enter data and perform a further case review. The team comprised of a consultant orthopaedic surgeon and myself. All data were entered into excel to enable further analysis. Any obvious issues in care or service delivery were noted including clear errors or delays. Each case was then compared with best practice (NICE, 2016; Vascular Society, 2016) by a group of experts including members of the orthopaedic, vascular, diabetes and podiatry teams. Factors noted as contributory were placed into a framework and the frameworks for all amputations were compared looking for any identifiable root cause. The team identified any factors that made patients a high-risk for amputation, identified any barriers to care within the current system and discussed possible solutions.

NICE guidelines were referenced as gold standard management for care of the diabetes foot (NICE, 2016) and Vascular Society of Great Britain and Ireland guidelines were referenced as gold standard management for major lower limb amputation (Vascular Society, 2016). Care guidelines from ABMU were not available to compare current practice to in these cases.

3.3.3.3 Review team

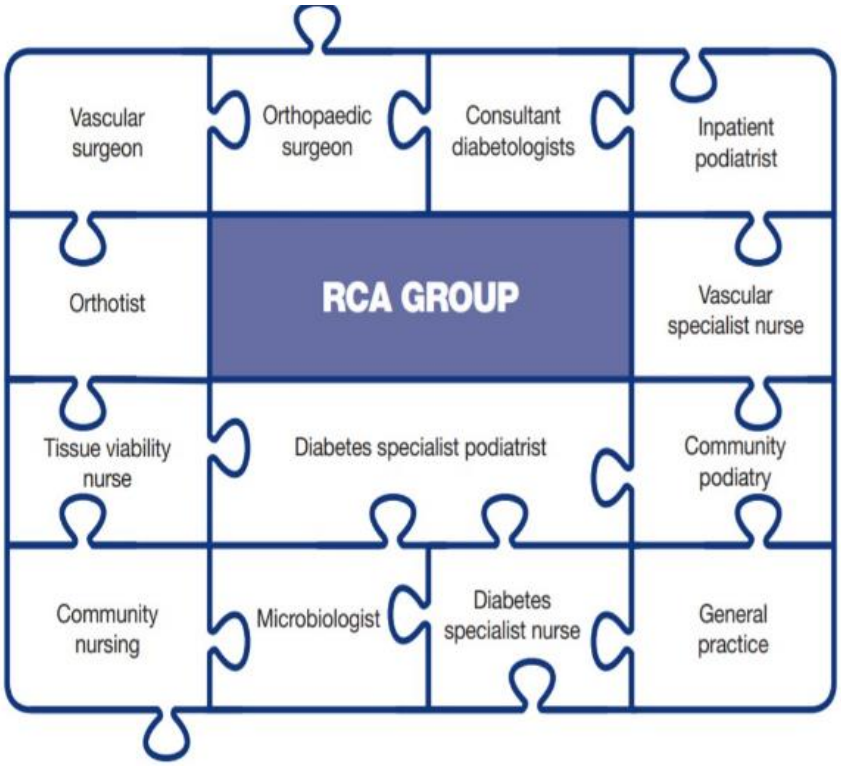
Care teams involved in patient admissions were invited to be involved in initial review process (Table 3.2). In the RCA guidelines from Diabetes UK and the NPSA it is suggested that all members of the foot care MDT team be involved in the RCA (Figure 3.3) (Diabetes UK, 2017). No formal MDT had been established in the health board prior to this review. Although all members that constitute a full footcare MDT (NICE, 2016) were present within Morriston hospital and involved in patient care, some members of staff were not available for the review and were not currently

acting as a formal MDT. GPs were able to give views on cases through the proforma but not directly in the review process.

Table 3.2. Members of the RCA review team

Investigation team
Orthopaedic team (Consultant, Registrar, Research fellow)
Vascular team (Consultant, Registrar)
Consultant Diabetologist
Primary and Secondary care Podiatry
IT support
Secretarial support

Figure 3.3. RCA group as recommended by Diabetes UK



Diabetes UK recommended members of the diabetes amputation root cause analysis team (Diabetes UK, 2017) accessed 01/04/2018.

3.3.4 Analysis

The first step of analysis was to determine direct causes of the event by asking why the incident had occurred. These direct causes are steps in care within the incident that were a divergence from the gold standard, such as delayed scans, missed appointments or delayed diagnosis. To explore contributory factors further, we used the modified contributory factors framework from the NPSA – RCA Toolkit (Appendix II) (NPSA, 2015). The choice of model used in incident investigation is of key importance as it can influence the data collected, analysis performed and investigation outcome (Lundberg, Rollenhagen, & Hollnagel, 2009). The NPSA framework was developed based on the contributory factors framework developed by Vincent et al (C. Vincent, Taylor-Adams, & Stanhope, 1998). The development of the contributory factors framework was based on the idea of the Swiss Cheese Model of accident causation and Reason's (2008) work on accidents within organisations. It was the first attempt to produce a systematic and replicable method to understand all factors contributing to an adverse incident within healthcare, expanding on prior models which focused only on the impact of the professionals involved with an event (C. Vincent et al., 1998). The model adds consideration of the contribution of divergence from expected function of technology and environmental conditions (Hollnagel, 2004). The NPSA framework splits the contributory factors into categories allowing those conducting the study to further ask 'why?'; those used within the study are described in Table 3.3.

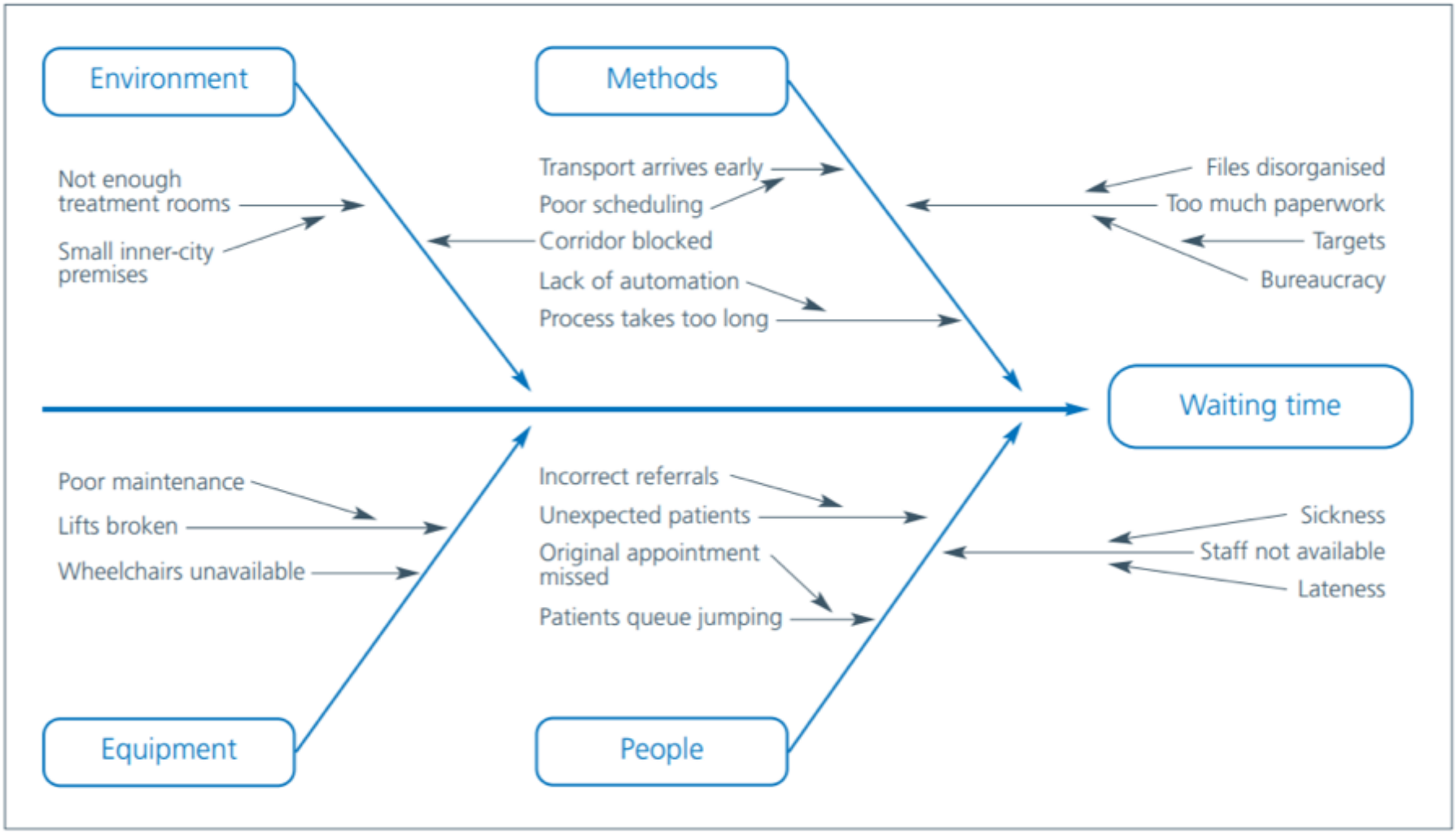
Defining groups of contributory factors allows for consistent collection and collation of casual data, which creates comparable outcomes from individual cases. Making the process consistent allows for a greater chance of highlighting actionable issues across a case series. These factors are further defined into influencing or casual factors. Influencing factors are those that may have influenced an incident, but the incident would likely have occurred in any event. It may be that modifying these issues will improve an outcome, or safety of a system but would not prevent recurrence of the investigated incident. Factors that led directly to the incident are defined as casual factors. Removing or modifying these factors would likely have prevented the incident or will prevent recurrence of incidents in the future (NPSA, 2015).

Table 3.3. Descriptions of primary factor categories within the contributory factors framework, adapted from Dineen (2002)

Factor Category	Description
Patient	Unique to patient or patients - relate to severity of disease, co-morbidities and patient related psychological, cultural and social issues.
Task	Related to effective and safe delivery of healthcare processes.
Communication	Written or verbal that affect performance or task completion.
Team	Management styles, hierarchy and how staff and others perceive role and its effect.
Education and training	Effect of any gaps in knowledge or supervision from training on event outcomes.
Equipment and resource	Functionality and availability of equipment and staffing levels.
Working conditions	Environmental issues including noise, heating and overcrowding.
Organizational and Strategic	Underlying cultural beliefs, behaviors and principles within an organization which impact care provision.

Once factors had been identified and grouped and their effect had been determined, information for all cases was collated to help visualise recurrent issues. The three most widely used tools for visual analysis of a case series are the cause and effect diagram (CED), the interrelationship diagram and the current reality tree (Doggett, 2006). The visual representation of the problem and relationships can help organize and focus group thinking. The CED was selected for use within the study. It is more commonly known as the Ishikawa fishbone diagram (Wong K.C., 2016). The diagram consists of a trunk, which represents the problem, and branches which represent the causative factors. Further branches 'twigs' from the tree represent each factor contributing to those causative factors (Figure 3.4) The final diagram gives a visual representation of the problem but does not identify a single definitive root cause. This decision to identify a single root cause can be made by the analysing team or the analysis can be left with multiple contributory factors.

Figure 3.4. Example fishbone diagram



Example fishbone diagram: Waiting time represents the issue with the environment, equipment, people and methods the causative factor 'branches' and the other text the contributing factors 'twigs' https://improvement.nhs.uk/documents/2093/cause-effect-fishbone.pdf (accessed 01/04/2018)

3.4 Results

3.4.1 Data access

At the final analysis, 7 sets of notes remained outstanding: - 2 sets were in clinical use, 2 remained in central storage (not retrieved after 8 months), 2 were unavailable from another hospital after earlier volumes had been destroyed and 1 set was lost. The secondary care notes containing the amputation admission were available for 68 (94%) of the cases. Consent for review of primary care notes was given or presumed for 62 (85%) patients. A direct GP response was obtained in 23 (37%) cases and the amputation history from primary care was accessed primarily through the WCP in 48 (77%) cases. Of the 23 GP responses 15 provided comprehensive information. The 8 GP responses with limited information (Table 3.4) were reviewed further using the WCP. In addition, 21 (29%) sets of ABMU secondary care podiatry notes were reviewed. The community podiatry pathway was accessed in 18 (25%) of the cases and further information on podiatry input and foot risk was obtained through clinic letters available on the secondary care diabetes database (Leicester database). Access to Neath Port Talbot primary or secondary care podiatry notes were not available at the time of review, therefore it was not possible to comprehensively assess the impact of podiatry in the root cause analysis.

Table 3.4. Reasons for limited GP information

Reason for limited GP response
Little or no GP attendance
Nursing home care
New patient to practice
Under secondary care diabetes review

3.4.2 Patient characteristics

During this review process, 4 further amputations were excluded as they did not meet the inclusion criteria. One patient underwent amputation secondary to traumatic crush injury with major muscle necrosis, 1 amputation was due to an open ankle fracture with complications, 1 was an elective procedure for longstanding pain after failed ankle arthrodesis and 1 AKA was for an infected total knee replacement (a plastic surgery procedure).

This left 75 procedures on 72 patients for analysis. Table 3.5 displays the baseline characteristics of the patients. The median age at amputation was 71 years (range: 40-89 years) and the majority were men (69%). The majority of patients were living in their own residence at the time of admission (86%) and had social support available (74%), with only 1 patient requiring carers in the community prior to admission.

All patients had at least one co-morbid condition at the time of admission (Figure 3.5) with 87.5% known to have a diagnosis of PVD. At admission, 34 of the patients (47.2%) had a documented recent acute illness unrelated to their diabetes related foot disease, indicating the frailty of the cohort.

At time of review 39% (28) patients were deceased (Appendix II-Gannt chart 7). This was in keeping with the national estimates of a 50% mortality at 5 years after amputation. Ten (14%) patients died during the amputation admission.

Table 3.5. Demographic and admission data for patients undergoing major amputation.

Category		n (%)	Category		n (%)
Age		71 (40-89)*	Social support	Available	53 (73.6)
Gender	Men	50 (69.4)		Lives alone	11 (15.3)
Health board	Abertawe Bro Morgannwg	48 (66.7)		Active carer	1 (1.4)
	Hywel Dda	24 (33.3)		Unknown	7 (9.7)
Residential status	Own home	62 (86.1)	Diabetes control	Adequate[x]	14 (19.4)
	Nursing home	2 (2.8)		Poor	48 (66.7)
	Residential home	3 (4.2)		Unknown	10 (13.9)
	Unknown	5 (6.9)	Amputation Cause	PVD	36 (50.0)
Admission location	Home	48 (66.7)		PVD & sepsis	24 (33.3)
	Transfer	21 (29.2)		Osteomyelitis	8 (11.1)
	Unknown	3 (4.2)		Acute embolus	2 (2.8)
Admission route	GP	13 (18.1)		Lymphoedema	1 (1.4)
	Emergency Department	9 (12.5)		Sepsis & venous insufficiency	1 (1.4)
	Podiatry	6 (8.3)	Amputation type	Below Knee Amputation	45 (62.5)
	Other	38 (52.8)		Thru Knee	3 (4.2)
Admission speciality	Vascular	58 (80.6)		Above Knee Amputation	24 (33.3)
	Orthopaedic	4 (5.6)	Operating speciality	Vascular	65 (90.3)
	Diabetes	1 (1.4)		Orthopaedic	7 (9.7)
	General Medicine	9 (12.5)			
Marital status	Married/Partner	42 (58.3)			
	Single	23 (31.9)			
	Unknown	7 (9.7)			

PVD: Peripheral Vascular Disease; GP: General Practice, *year, X adequate diabetes control defined as previous three available HbA1c within range defined for patient or comment of adequate control within patient notes, poor diabetes control defined as less than three previous available HbA1c within range defined for patient or comment of poor control in patient notes.

Figure 3.5. Co-morbid disease other than diabetes mellitus at time of admission for Major Amputation

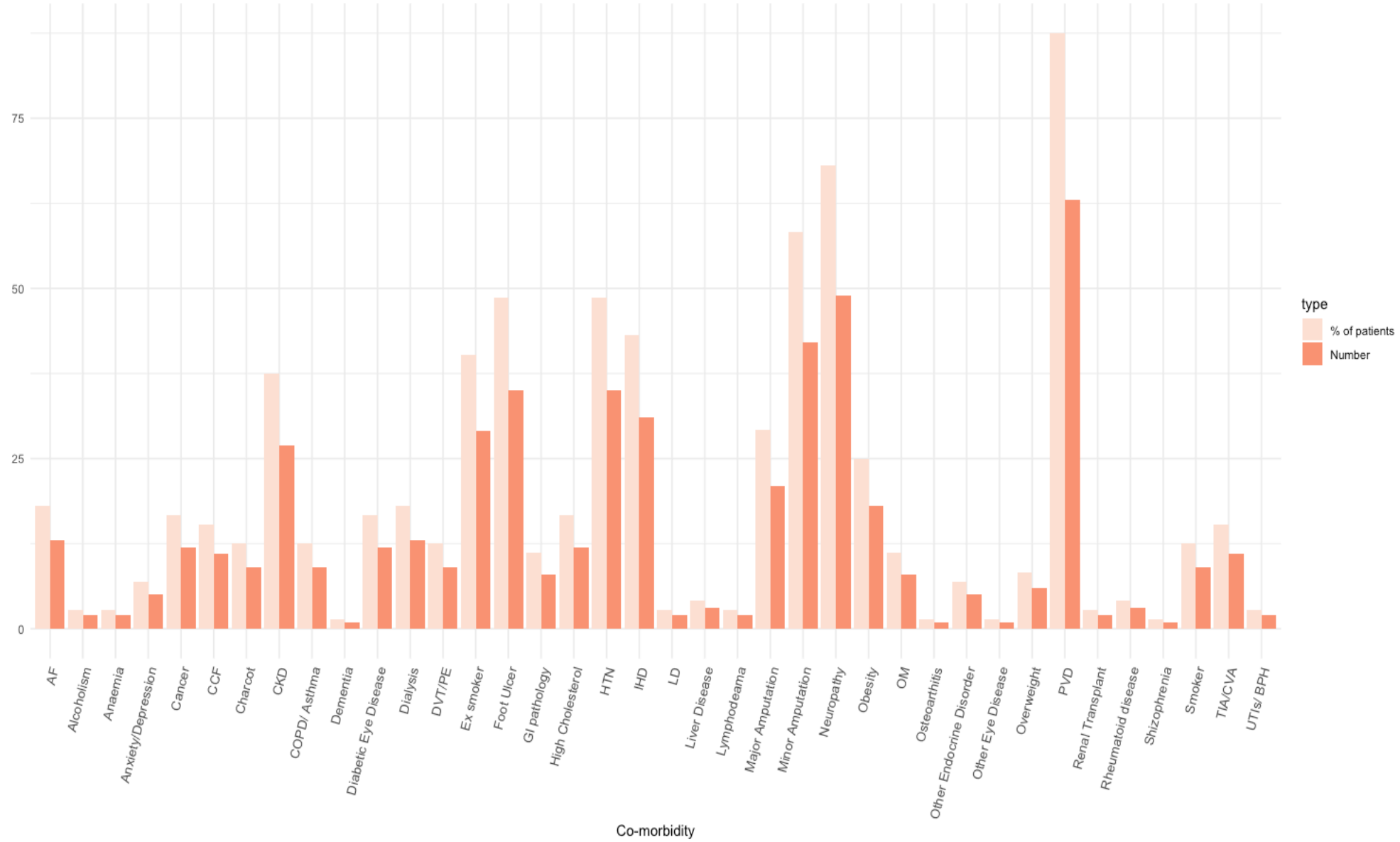


Figure 3.3: Number of patients with condition in orange, Percentage of 72 patients in peach. AF: Atrial fibrillation; CCF: Congestive Cardiac failure; CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary disease; DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism; GI: Gastrointestinal; HTN; Hypertension; IHD; Ischaemic Heart Disease; LD; Learning difficulty; OM: Osteomyelitis; PVD: Peripheral Vascular; TIA; Transient Ischaemic Attack; CVA; Cardiovascular accident; UTI: Urinary Tract infection; BPH: Benign Prostate Hypertrophy

3.4.3 Case Characteristics

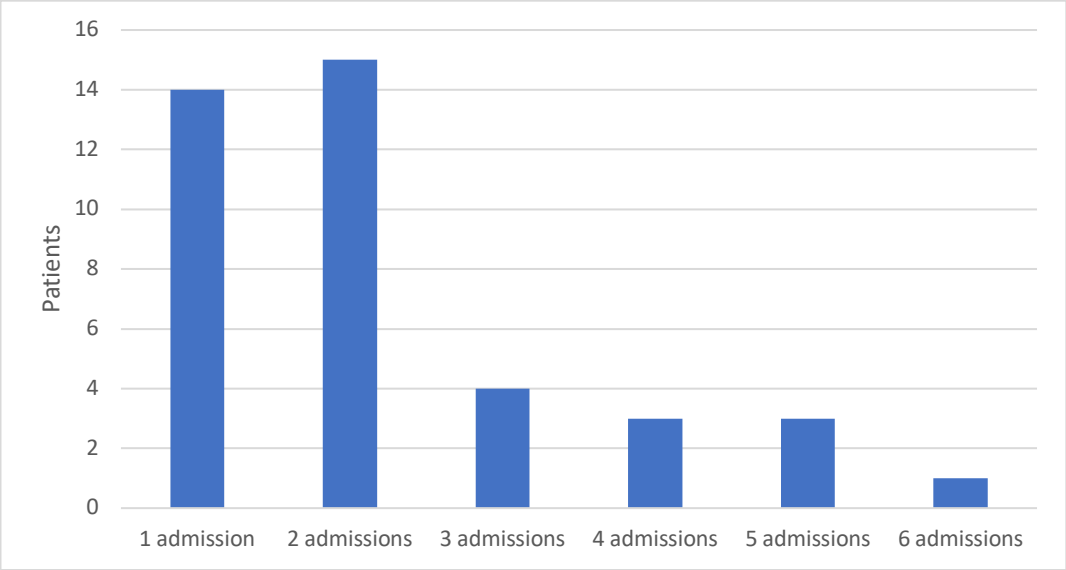
In 83% (60) of the cases, PVD with or without sepsis was found to be the primary aetiology leading to amputation. Osteomyelitis was present in 8 cases (11%), 2 patients presented with an acutely ischemic limb secondary to an embolus (3%), 1 patient presented with lymphoedema and 1 patient had sepsis secondary to venous insufficiency. An ulcer was present on admission in 66 cases (92%). The majority of amputations were forefoot 28 (42%), 16 (24%) were digit, 17 (26%) heel and 5 (1%) midfoot. An ulcer in another pressure area such as the sacrum was noted in 10 cases. Notes were examined for ulcer classification scores. No admission notes demonstrated clear documentation of a Site, Ischaemia, Neuropathy, Bacterial Infection and Depth (SINBAD) score and a Waterlow score was only documented in 12. For the 69 patients where admission documentation was available for review, foot assessment was performed within 24 hours of admission for 62 of the patients (86%), in keeping with the NICE guidelines (NICE, 2016).

The median length of time from initial foot problem to admission was 311 days (range: 10-4019 days) with the median length of time from initial foot problem to amputation 314 days (range: 14-4036 days); excluding the 1 patient who developed an index foot issue within the amputation admission. The median amputation admission length was 29 days (range: 6-175 days) and the median time from admission to amputation was 6 days (range: 0-85 days).

Podiatry data were available for 28 (39%) patients. Over half the patients were known to podiatry prior to development of an issue in the foot requiring amputation (57%). For patients known to podiatry at any stage the median length of foot disease prior to amputation admission was 469 days (range: 29-3638 days). The median time from foot disease to amputation was 477 days (range: 59-4036 days), 5.5 months longer than those who were not known to podiatry.

Recurrent admissions were common in the cohort (Figure 3.4); 40 (56%) patients were documented to have had a least one acute admission secondary to a foot problem within the health board prior to admission for their major amputation. Culminating in a total of 89 admissions and 2022 inpatient days (5.5 years) for 40 patients.

Figure 3.6. Number of admissions per patient for foot disease prior to the major amputation admission.



Including the major amputation admission this gave a total of 161 admissions, with a total length of 4841 days (13.3 years) for the entire cohort. The median total number of days in hospital per patient within an admission associated with diabetes-related foot disease was 51 days (range: 6-294 days).

In 69 cases the vascular surgical team were the primary care providers on the major amputation admission; in 89% of cases the patients were previously known to the vascular team. In the 7 cases where the patients were not known to the vascular team prior to the event, 3 had previously been seen by a podiatry team. Four patients had not been referred to any secondary care services prior to the amputation admission.

Of the patients known to the vascular team prior to the major amputation admission, 38% first presented in an outpatient setting, 31% first presented in an acute admission that did not involve surgery and 31% had first contact through an acute admission that involved a debridement or amputation procedure. In the 62% of cases where patients had first presented to the vascular surgical team through an acute admission prior to their major amputation admission, 17 (47.2%) had no documentation of referral to any speciality within the acute foot care MDT prior to the

acute admission. The remaining patients had previously been reviewed in podiatry (15 patients), a secondary care diabetes clinic (8 patients) or by an orthopaedic team (4 patients).

In the patients where major amputation admission was under the vascular surgical team, 27 (39.1%) had been reviewed by the vascular team prior to the development of the disorder leading to the major amputation within the review i.e. for issues in the other limb/ previous revascularisation. The median time from first vascular review to development of the foot problem leading to amputation was 891.5 days (range: 69-8400 days) and the median time to admission from first vascular review was 1192 days (range: 160- 9825 days).

For 22 patients, the first time they were reviewed by the vascular surgical team was for the foot problem leading to amputation. In 21 cases this was prior to the admission for their major amputation. For these patients the median time known to the vascular surgical team prior to the amputation admission was 453 days (range: 27-3638 days). In 6 cases the first review by the vascular team was during the major amputation admission.

For 16 patients, there was documentation that the foot problem leading to amputation was noted in primary care or by another secondary care provider and then referral to the vascular team was made. The median length of time the foot problem was present prior to referral was 119 days (range: 4-1461 days). The median time to amputation admission after vascular review was 40 days (range: 0-1884 days).

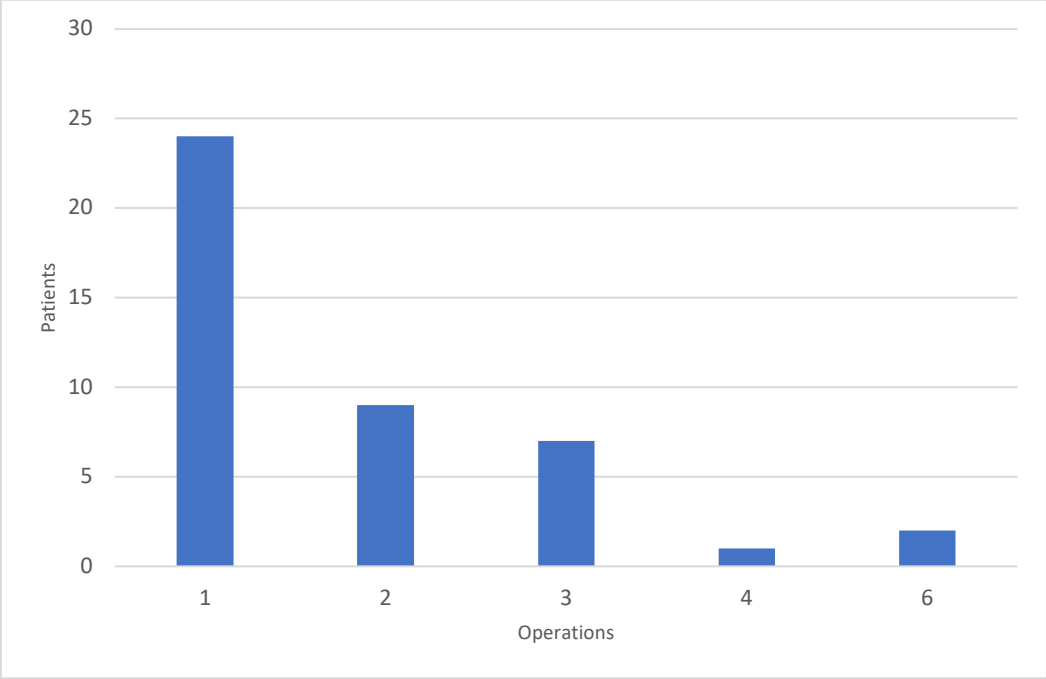
In total, 40 patients had been reviewed in vascular outpatients prior to the major amputation admission. Information on the referral was available for 24 cases; the median time from referral to review was 21 days (range: 0-242 days). Most patients were reviewed one or two times prior to their major amputation admission. For inpatient reviews, most patients were reviewed by a member of the vascular team on the same day if a referral was requested (40 of 54 requests) with the greatest delays 7 and 9 days. Thirty-five patients were noted to have been discussed at vascular MDT, 17 pre-admission and 18 during admission.

The orthopaedic team reviewed six patients in a clinic prior to their amputation admission; the time from request to review was not available. Of the 12 patients that required inpatient orthopaedic review the mean time from referral to review was 1 day (range: 0-4 days) with 75% reviewed on the same or following day.

3.4.4 Previous Procedures

A single revascularisation procedure attempt on the ipsilateral limb was made by interventional radiology or the vascular surgical team prior to the major amputation for 28 patients (39%). Eight patients (11%) had a history of two attempts. Graft failure prior to amputation was noted in 8 cases. Previous revascularisation attempts in the contralateral limb had occurred in 10 cases. Previous foot debridement and minor amputations were common in the cohort, with 43 patients (60%) undergoing a total of 79 minor amputations or debridement procedures prior to their major amputation. Frequency of amputation is shown in Figure 3.5

Figure 3.7. Frequency of minor amputation procedures prior to major amputation.



Several patients had undergone previous major amputations including revision procedures; 18 patients had undergone one pervious procedure; 2 patients had undergone two and 1 patient

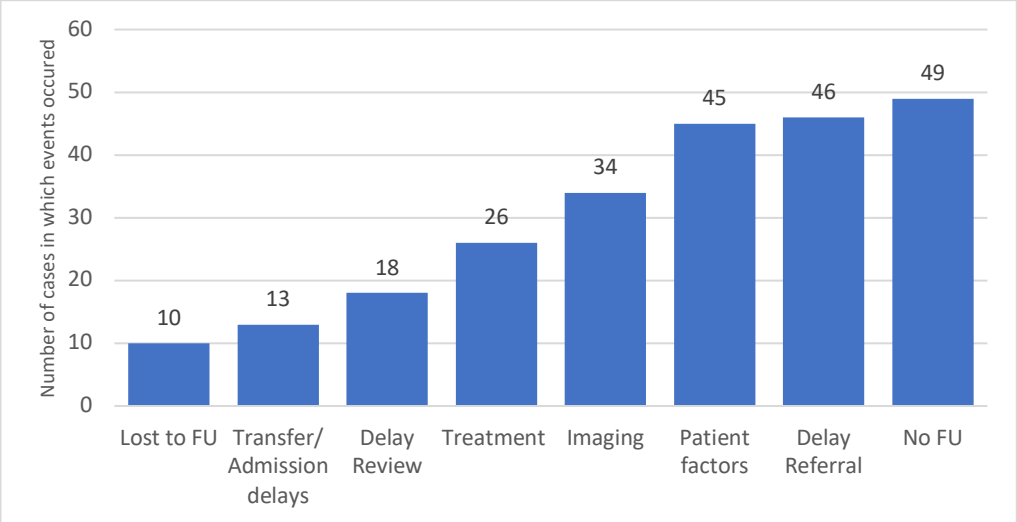
had undergone three. The average time between the major amputation prior to the major amputation within the review was 601 days (range: 9-3639 days). Eleven patients then went on to receive a subsequent major amputation following the major amputation within the review, 6 were on the contralateral limb and 5 were conversion of BKA to AKA in the ipsilateral limb. Three patients received bilateral amputation within the same year. By the end of the review period 26 (36%) patients were bilateral amputees.

3.4.5 Analysis of amputation event

From the initial data analysis, the review team concluded that in 8 (10.7%) cases it was clear the amputation could have been prevented if the gold standard of care had been followed. In 58 cases (77.3%) prevention may have been possible and in 9 (12.0%) cases the amputation was viewed as unavoidable. For the 72 amputations, 52 different direct events were identified after group review (Figure 3.8). Direct events were classified as occurrences where care deviated from the gold standard. In total there were 249 direct events that deviated from the standard of care across the cases. In all cases, even those amputations deemed unavoidable, direct events were found within the review. The mean number of direct events identified per case was 3 (range: 1-7 events). The median number of direct events was higher in those cases deemed absolutely or possibly preventable compared to those deemed unavoidable.

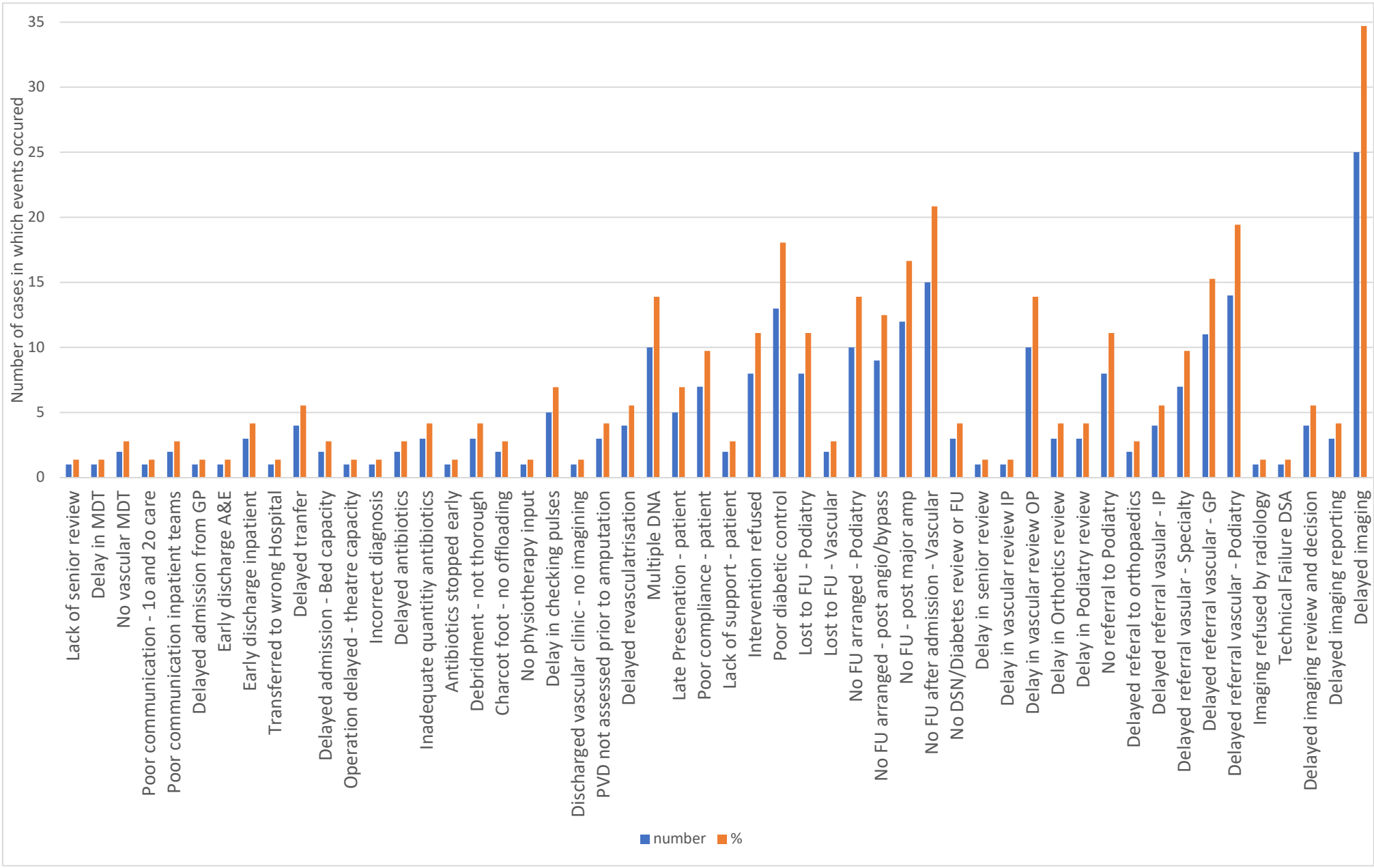
The direct events found fell into eight main categories. Events related to follow up (49 events), delayed referral (46 events) and patient factors (45 events) were found in the greatest proportion of cases (Figure 3.9).

Figure 3.8. Frequency of direct event categories identified in RCA



FU : Follow up

Figure 3.9. Direct events associated with root cause analysis - categories spilt into constituent parts

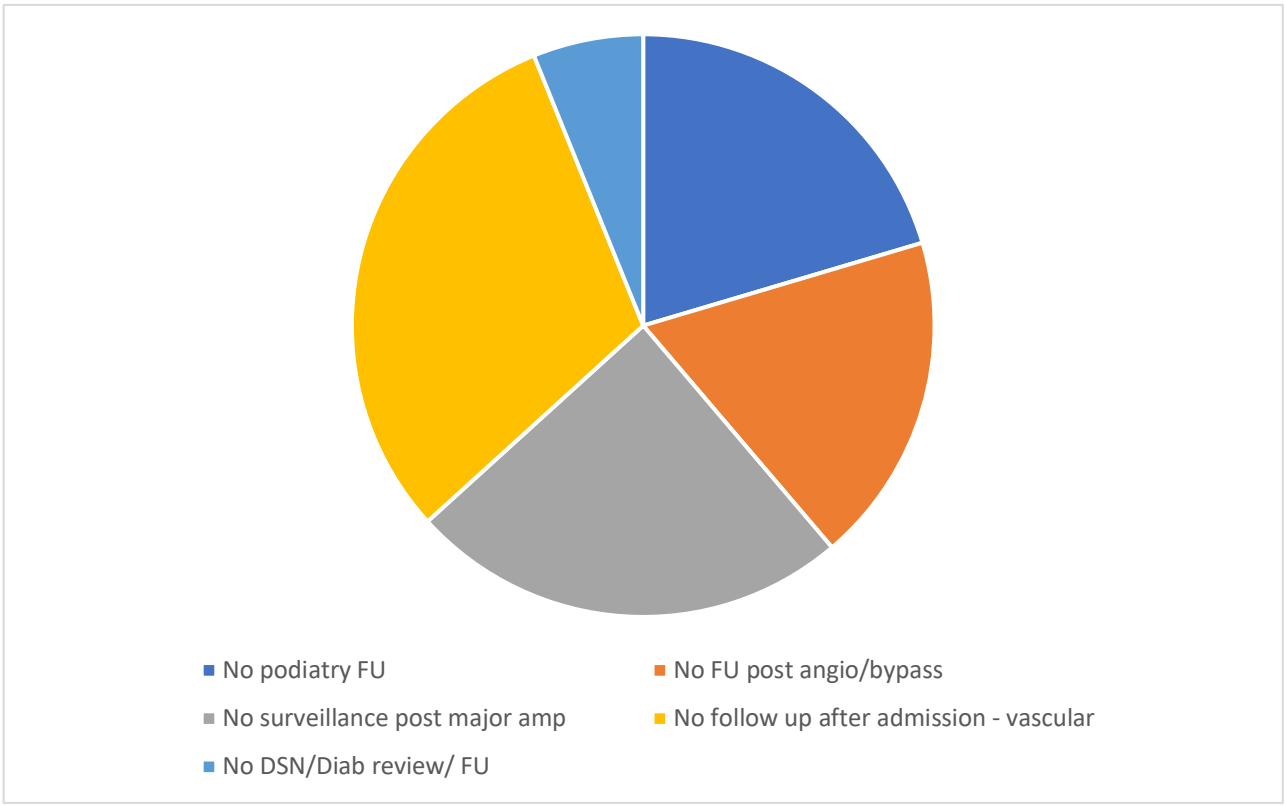


MDT: Multidisciplinary team; 1°: Primary; 2°: Secondary; GP: General Practitioner; A&E: Accident and emergency; PVD: Peripheral vascular disease; DNA: Did not attend; FU: Follow up; DSN: Diabetes Specialist nurse; IP: Inpatient; OP: Outpatient; DSA: Digital subtraction angiography.

3.4.5.1 Lack of follow-up

A lack of follow-up was found to contribute to amputation outcome in 49 cases (Figure 3.10). Events in this category consisted of a lack of follow-up for patients with a high foot risk, when assigning risk based on NICE guidelines (NICE, 2016), by any clinical speciality in a recommended multidisciplinary foot care team. No podiatry follow-up was noted in 10 cases, no vascular follow-up after amputation, intervention, or admission in 36 cases and no diabetes or diabetes specialist nurse review in 3 cases. In some cases, there was no clear documentation of referral to podiatry or the diabetes team or there was no clear documentation that follow-up was arranged after admissions or procedures. In cases where there was documentation of referral; some referrals were lost, or appointments just did not occur.

Figure 3.10. Distribution of cases with lack of follow up identified as a direct event



FU: Follow up; DSN: Diabetes specialist nurse; Diab: Diabetes; Angio: Angioplasty.

3.4.5.2 Delayed referral

Delayed referral contributed to amputation outcome in 46 cases (Figure 3.11). Events in this category were defined as events where a delay in referral occurred when compared to the recommended guidelines in the opinion of the review team. This was noted within and across primary and secondary care and across specialities. A delayed referral to the vascular surgical team from podiatry was noted in 14 cases, from primary care in 11 cases, from another speciality in 7 cases and from another inpatient team in 4 cases. A delayed referral to orthopaedics was noted in two cases and a delayed referral to podiatry from a primary or secondary care team was noted in 8 cases.

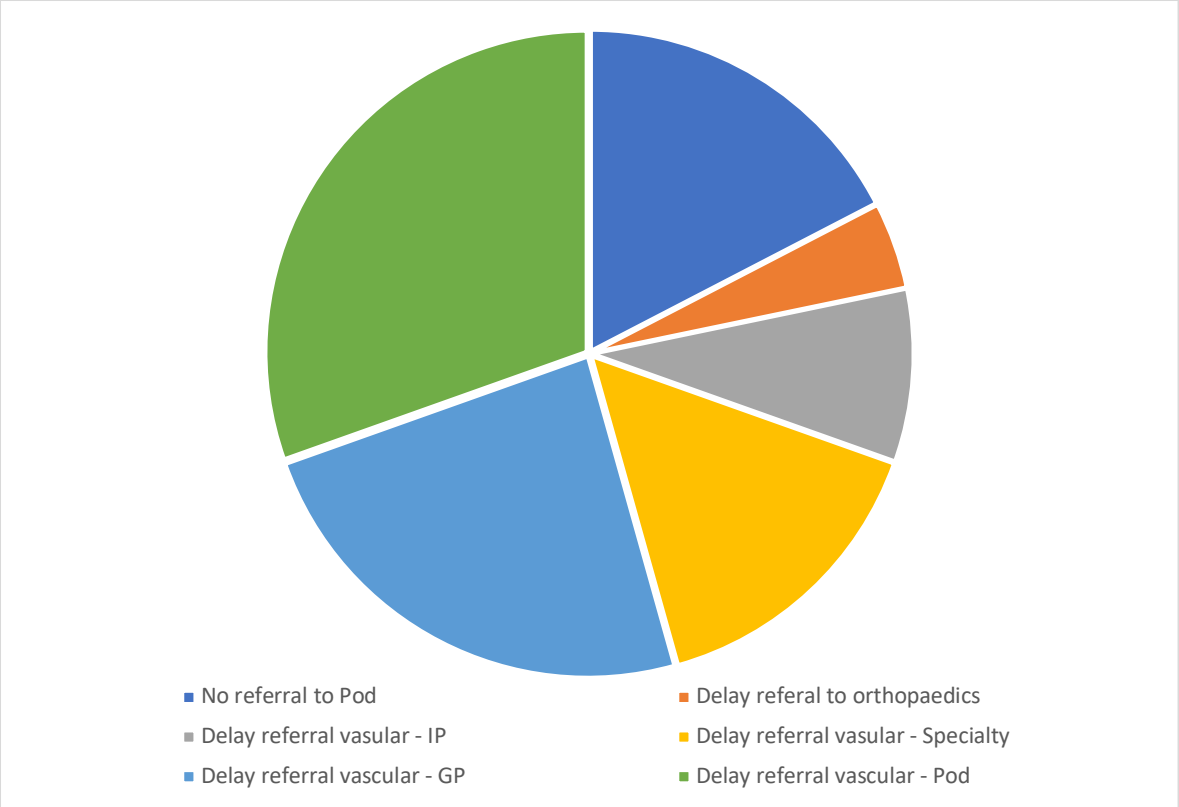
In the available GP data, appropriate referral at initial presentation after identification of a high-risk foot occurred for 2 patients. In 4 cases (Figure 3.12) delayed referral was noted. The median time from primary to secondary care review was 1192 days (range: 42-3270 days). For the patient with the longest delay their first contact with secondary care was through an acute admission for a foot problem.

From the available notes 10 patients presented for the first time to podiatry with ischaemia or reduced arterial flow in either limb. Referral within the recommended time frame occurred in 4 cases. In 6 cases (Figure 3.13) referral was delayed; with 1 patient attending for review with severe PVD on 2 occasions without referral. For these patients the median time from podiatry review to appropriate referral or secondary care review was 857 days (range: 72-3926 days).

There was also delayed referral noted from within secondary care. From all primary, podiatry and secondary care specialities, the median length of documentation of a foot problem to a vascular referral was 119 days (range: 4-1461 days) and the median time to amputation admission after vascular review was 40 days (range: 0-1884 days). In 6 cases the first review by the vascular team was during the amputation admission despite meeting criteria for referral from another team at an earlier point.

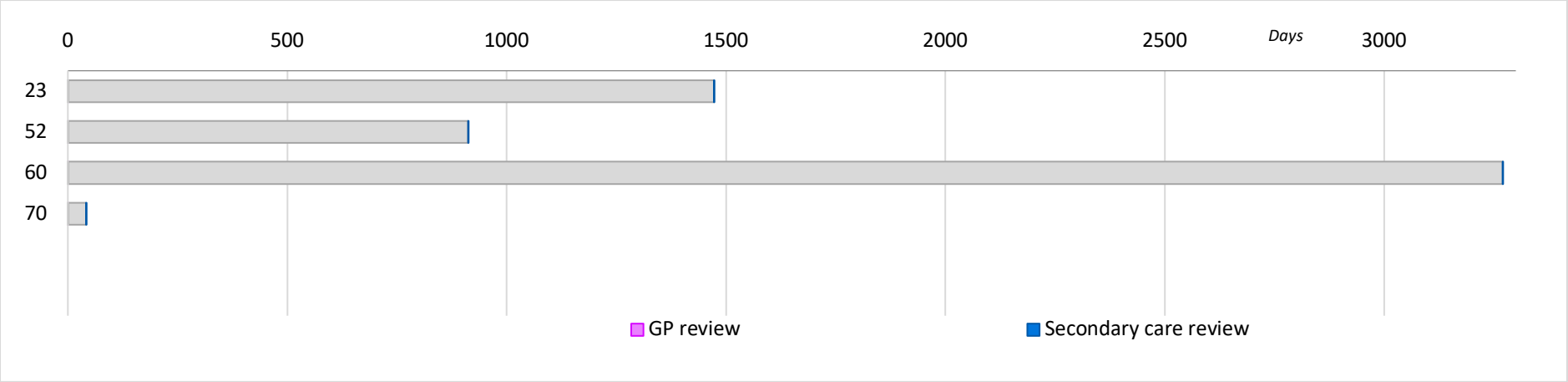
Of the patients whose first contact with the vascular team was through an acute admission (36 patients), 17 had no documentation of referral to any member of an acute foot care MDT prior to the amputation admission. Fifteen patients were known to podiatry, 8 were known to a Swansea diabetes clinic and 4 were known to orthopaedics. Excluding the patient where notes were not available, for 21 patients (29%) the first contact with secondary care was through an acute admission due to foot disease, this is suggestive of a delayed presentation to secondary care. In some cases, this was due to late patient presentation with a foot problem, with those patients not seeking medical care prior to the acute admission or from delayed referral from GP or community podiatry.

Figure 3.11. Distribution of cases with delayed referral identified as a direct event



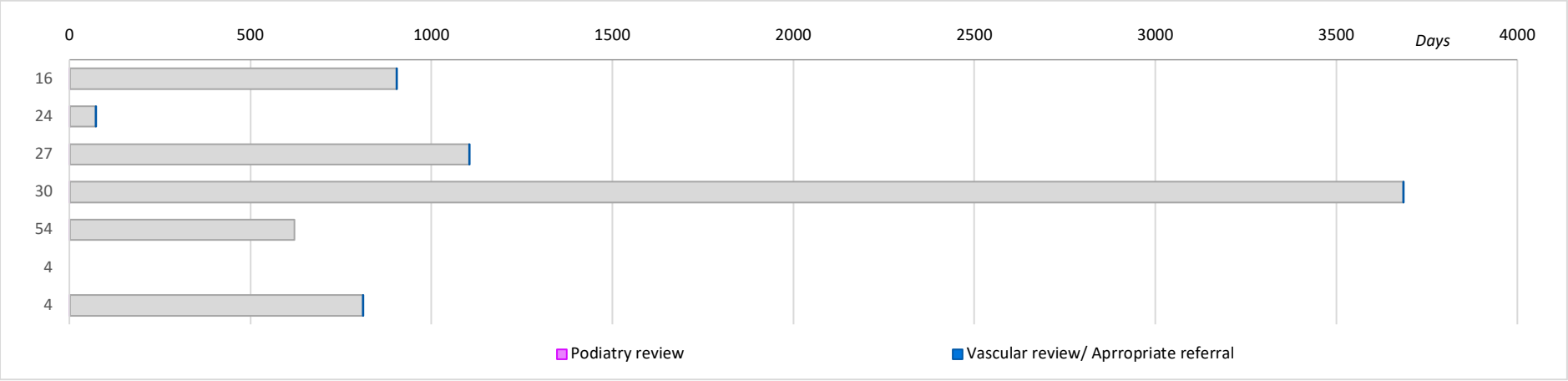
Pod: Podiatry; IP: Inpatient team

Figure 3.12. Gannt chart depicting time from GP review to secondary care review



Case number displayed on y-axis and days in pathway displayed on x axis. GP: General Practice

Figure 3.13. Gannt chart depicting time from podiatry review to vascular review/referral

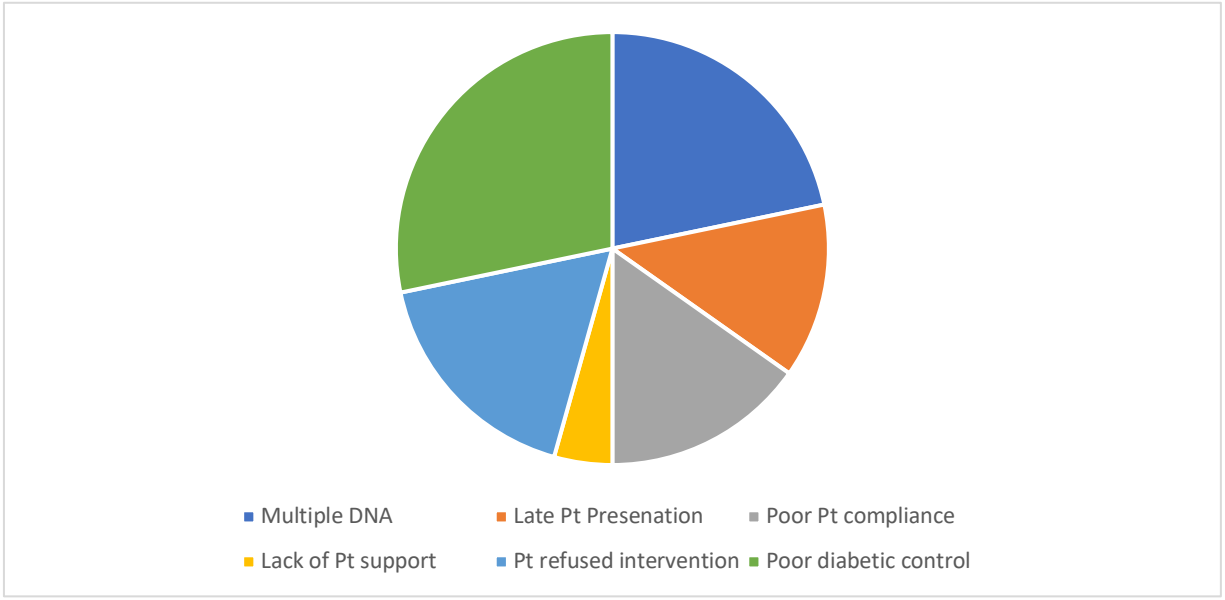


Case number displayed on y-axis and days in pathway displayed on x axis.

3.4.5.3 Patient Factors

Patient factors were identified in 45 cases (Figure 3.14). Events in this category were defined as events where the way in which patients engaged with services was felt to affect outcome. Multiple missed appointments were noted in 10 cases; 7 patients were noted to have multiple appointments where they did not attend (DNA) in podiatry. In some cases, this led to a loss to follow-up. Late patient presentation with a foot problem to primary or secondary care occurred in 6 cases; the actual number of cases in which this occurred was likely higher if full access to initial GP visit documentation or podiatry notes were available for all cases in the review. When reviewing the available GP data for delays, in 1 case a patient had waited one year to present to primary care with an ulcer, another patient delayed presentation to podiatry with dry gangrene, in 1 case a patient presented with a month-long history of necrotic toes and one patient bandaged their painful foot instead of attending for medical review. In 13 cases it was felt that patients contributed to the amputation outcome due to poor diabetes control. In 7 cases patients had poor compliance with treatments, such as antibiotic use. Patients refused intervention such a antibiotic, debridement, minor amputation or chose amputation in 8 cases and lack of patient support in community or hospital contributed directly in 2 cases.

Figure 3.14. Distribution of cases with patient factors identified as a direct event



DNA: Did not attend; Pt: Patient

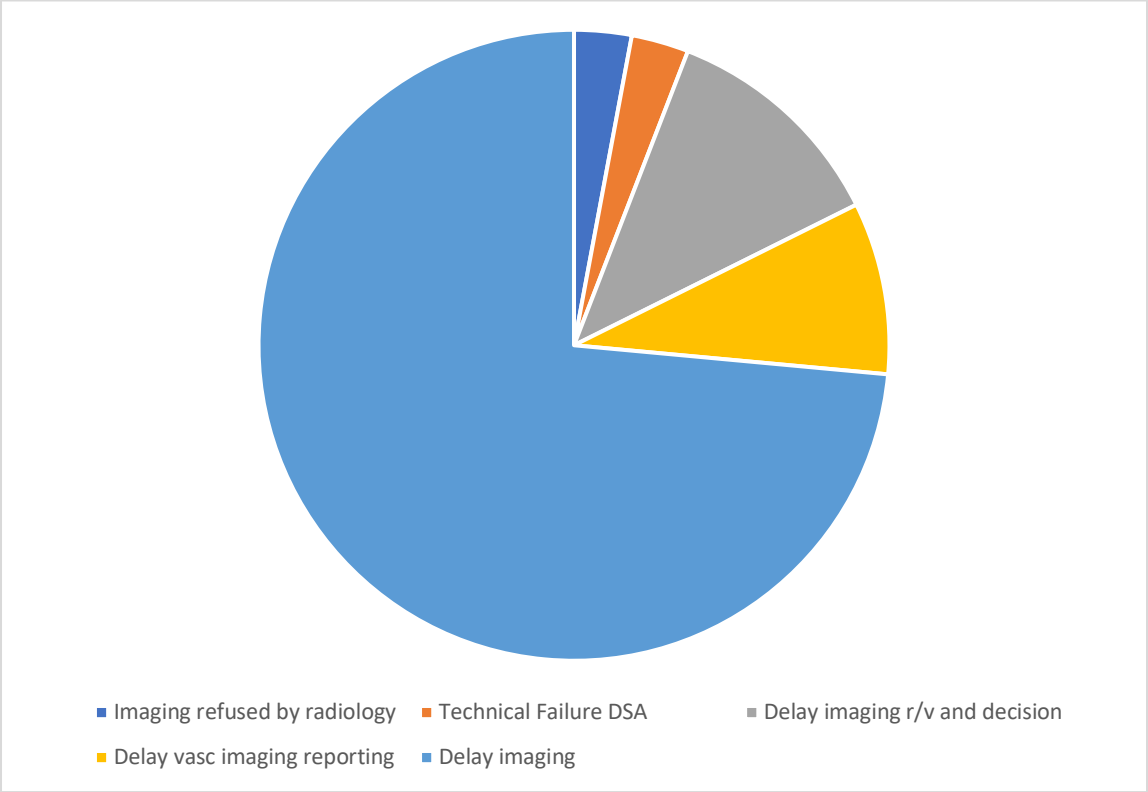
3.4.5.4 Imaging

Events relating to imaging were identified as a causative factor in 34 cases (Figure 3.15). Events in this category were defined when imaging was delayed or did not occur in the manner recommended in guidelines in the opinion of the review team. A delay in imaging was identified in 25 cases. Out of the 48 inpatient and outpatient CT angiography (CTA) of the aorta and lower limbs, the majority were performed on the same day or subsequent day with a median time to scan from referral being 1 day (range: 0-58 days) (Figure 3.16). The longest inpatient delay was 4 days.

The greatest delay in a case was 58 days in the outpatient setting; this was then followed by a one-month delay until review by the requesting team and action on the scan (Figure 3.17). Issues with imaging review and action were noted in 4 cases. Four CTAs were cancelled, 3 were due to the presence of previous imaging, but this was deemed inappropriate in one case. For the 19 MR angiograms of the aorta and lower limbs performed the median time from request to scan was 5 days (range: 0-41 days). Again, in the case with the longest delay this was followed by a long delay to review and action the scan (Figure 3.18). Fewer MRI scans of the foot were performed (11 scans), with the median time to MRI being 6 days (range: 0-46 days). The median time for inpatient scan was 4.5 days (range: 0-10 days). Only 1 patient received a scan within 24 hours as per guidelines (NICE, 2016). The cause of the 10 day delay was not clear from reviewing the notes.

Within the available information, only 28 patients (39%) had an ABPI or TBPI performed around or during the admission. Digital subtraction angiography of the lower limb was performed in 20 cases. The median time from request to scan was 6 days (range: 1-85 days) with the longest delay 85 days for an outpatient scan. In one case there was a failed attempt at revascularization due to a technical failure of the scanner.

Figure 3.15. Distribution of cases with events with imaging identified as a direct event



Vasc: Vascular; DSA: Digital subtraction angiography; r/v: review

Figure 3.16. Time from request to CT angiography scan occurrence.

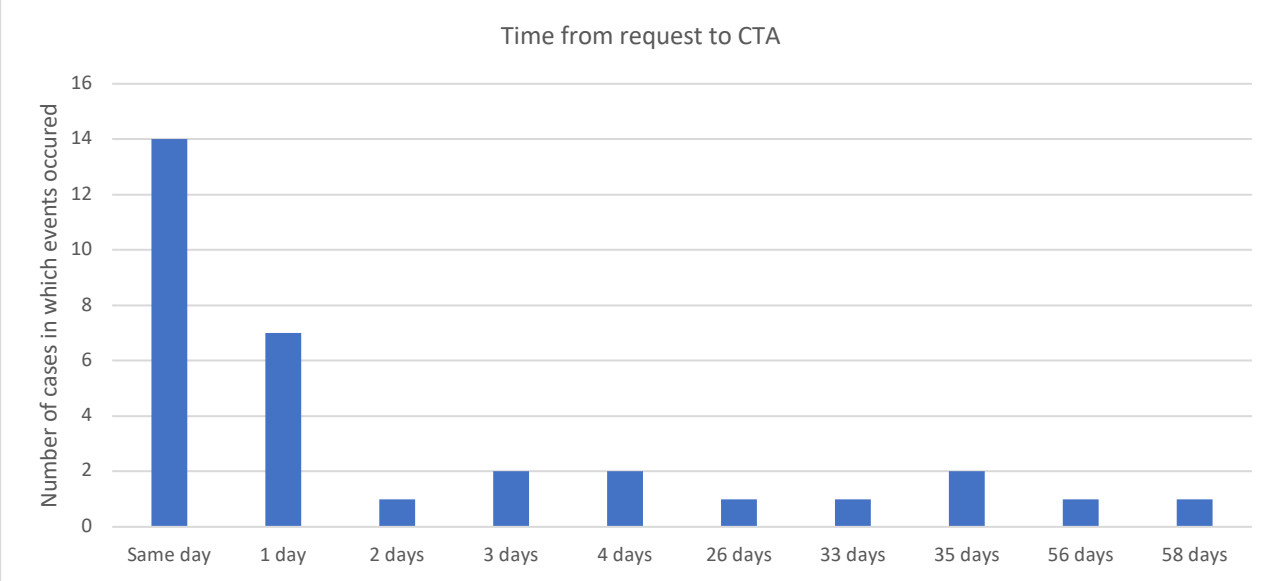
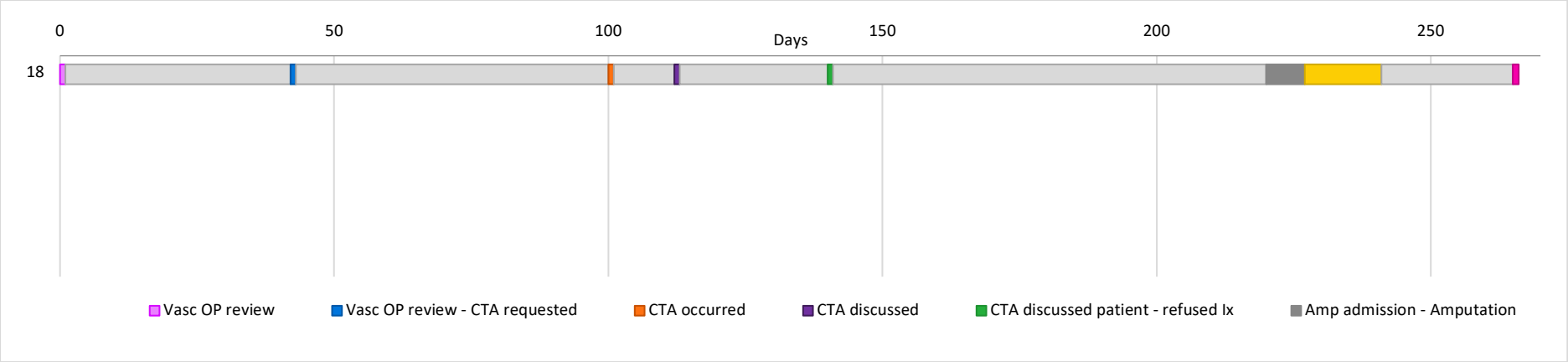


Figure 3.17. Amputation timeline for case 18 - showing a 58 day delay for CTA & a further 1-month delay until review & action



Case number displayed on y-axis and days in pathway displayed on x axis Vasc: Vascular; OP: Outpatient; CTA: CT angiography; Ix: Intervention; Amp: Amputation

Figure 3.18. Amputation timeline for case 19 - showing a 41 day delay for MRA & a further 3-month delay until review and action

Case number displayed on y-axis and days in pathway displayed on x axis GP: General Practice; Pod: Podiatry; ref: referral; Vasc: Vascular; MRA: Magnetic Resonance Angiogram; Amp: Amputation

3.4.5.5 Treatment

Treatment events were identified as a causative factor in 26 cases. Treatment events were classified when treatment was delayed or did not occur as recommended in guidelines in the opinion of the review team. There was a mix of events due to patient factors, diagnostic factors and treatment delays and mistakes (Table 3.6). The event that occurred in the greatest number of cases was a delay in checking pulses, this occurred within both the primary and secondary care settings.

3.4.5.6 Delayed review

Delayed review was identified as a causative factor in 18 cases (Figure 3.19). In 12 cases (17%) a delay in review in an inpatient or outpatient setting was noted. Of these, 1 patient refused referral, 4 patients had delays in vascular outpatient review with 1 patient waiting five months from referral. One patient was lost to follow up from vascular outpatients after an initial visit, 1 patient had delayed orthopaedic outpatient review due to scheduling and one patient was delayed in seeing an outpatient diabetes specialist nurse. A delay in orthotics review occurred in 3 cases and it was noted to be an issue raised by podiatry in the review process.

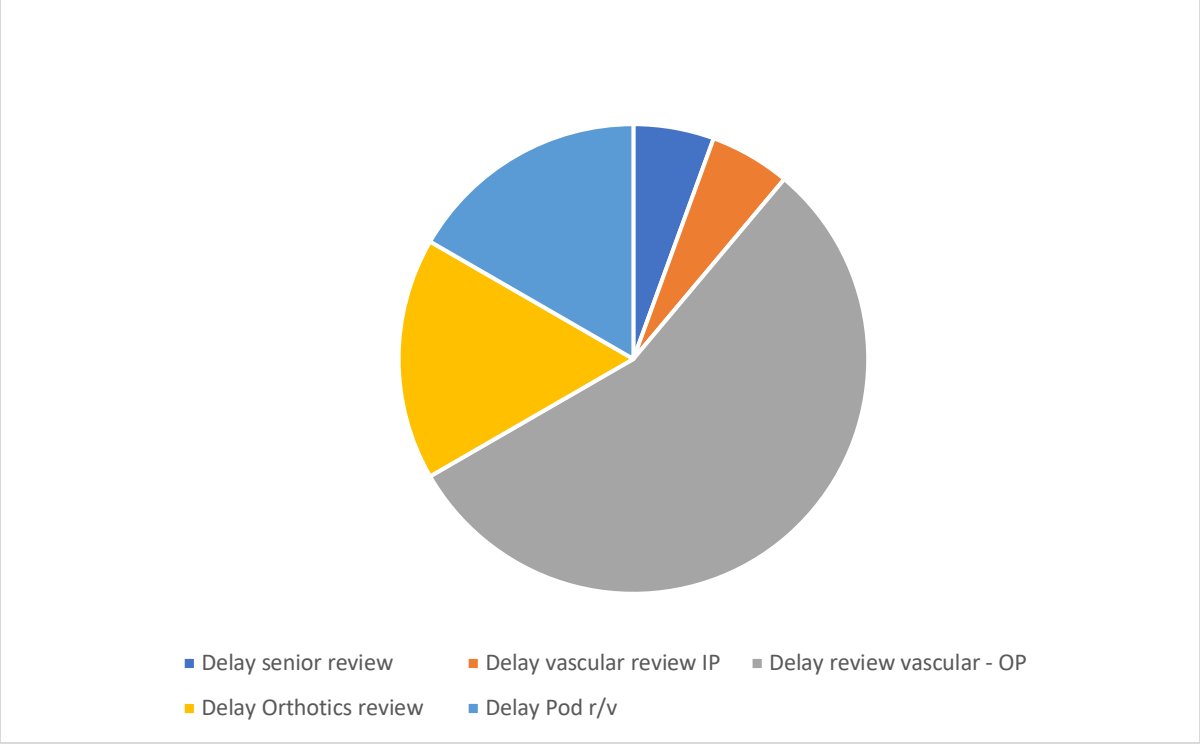
For inpatient referrals, most patients were reviewed by a member of the vascular team on the same day if a referral was requested (40 of 54 requests). Delays in inpatient reviews were all from the vascular team with 3 patients delayed for vascular inpatient review due to issues with transfer from another hospital. In 1 case the reason for delay was unclear. The greatest delays identified were of 7 and 9 days. For these cases the delays were due to patient location with one patient transferred to the wrong hospital from a different health board.

Although in most cases (81%) review by a senior member of the team occurred within 24 hours of admission, in 12 cases it was unclear if this had occurred and in 1 case it was clear a delay in senior review contributed to the outcome of the case.

Table 3.6. Distribution of cases with treatment events identified as direct events

Treatment factor	N	%
Incorrect diagnosis	1	3.8
Delay in giving antibiotics	2	7.7
Inadequate quantity antibiotics osteomyelitis	3	11.5
Antibiotics stopped early	1	3.8
Not thorough debridement	3	11.5
No offloading Charcot foot	2	7.7
Benefit from physiotherapy input	1	3.8
Delay in checking pulses	5	19.2
Discharged vascular clinic - no imagining	1	3.8
No assessment of vasculature prior to amputation	3	11.5
Delayed revascularisation	4	15.4

Figure 3.19. Distribution of cases with delayed review identified as a direct event.

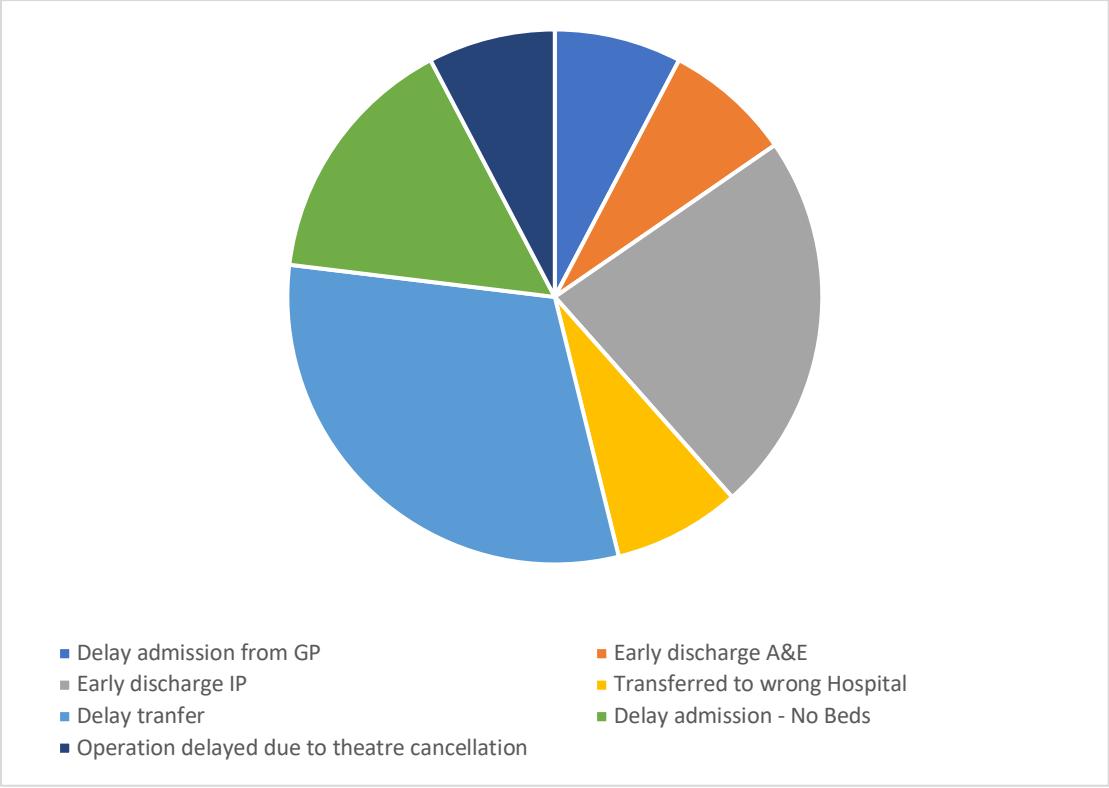


IP: Inpatient; Pod: Podiatry; r/v: Review; OP: Outpatients

3.4.5.7 Transfer/Admission

Issues with transfer or admission events were identified as a causative factor in 13 cases (Figure 3.18). A delay in transfer from a vascular spoke hospital to the hub occurred in 4 cases, early discharge without completion of treatment due to patient self-discharge or incorrect interpretation of clinical finding occurred in 3 cases. Delayed admission for a minor procedure or debridement due to bed capacity occurred in 2 cases. Delays in a debridement due to theatre cancellations occurred in one case, as discussed above a patient was transferred to the wrong hospital in one case leading to delayed treatment. A patient was inappropriately discharged from A&E in 1 case and in 1 case there was a delay in admission from GP due to transport availability.

Figure 3.20. Distribution of cases with transfer or admission events identified as a direct event.



GP: General Practice; IP: Inpatient; A&E Accident and Emergency Department

3.4.5.8 Loss to follow up

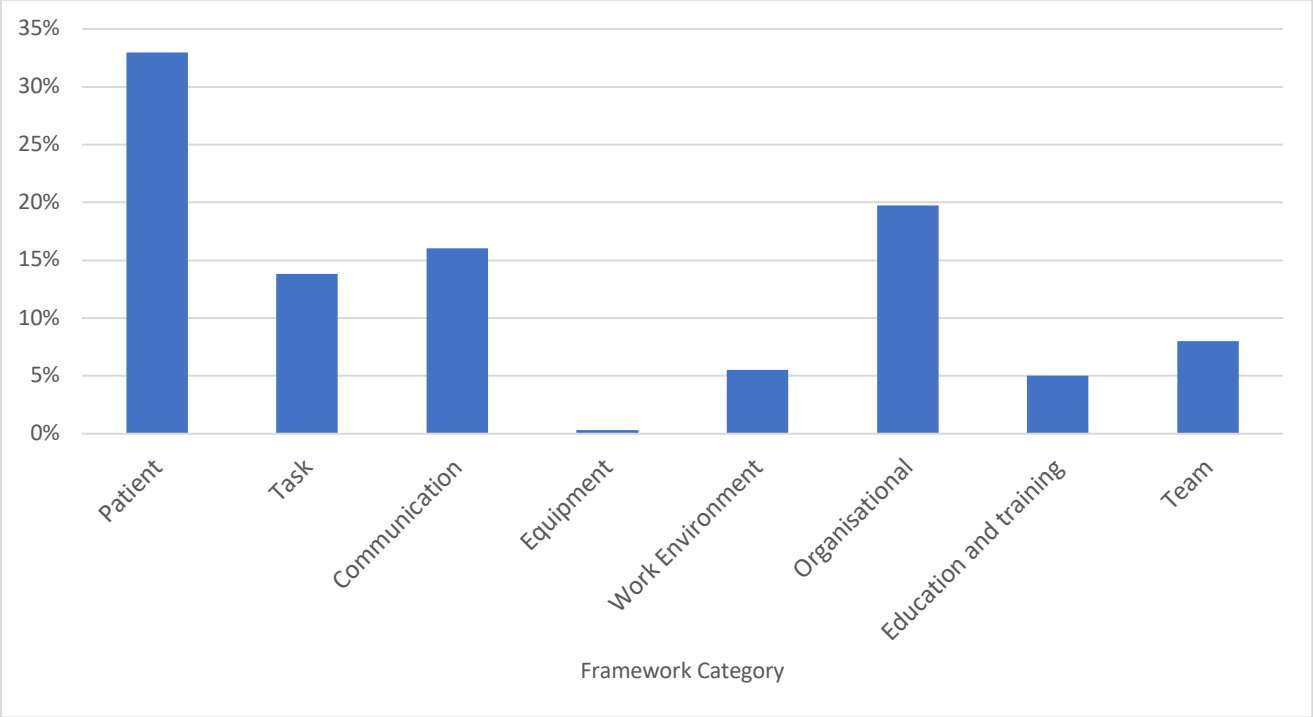
Loss to follow up was identified as a causative factor in 10 cases. This occurred after patient DNA, inpatient or outpatient appointment and was defined when follow-up was clearly documented as a requirement but did not occur. This occurred mainly in the secondary care podiatry service, where 8 patients were noted to be lost to FU at some point during the course of the diabetes foot disease episode. This constituted 29% of cases where podiatry services were utilised for which documentation was available. There was not information on podiatry input for all patients. In two cases patients were lost to vascular follow up.

3.4.6 Root causes – National Patient Safety Agency Framework

The NSPA framework was used to categorise contributory factors and identify in how many cases each contributory factor occurred. From the direct causes 59 individual root causes were identified within the contributory factors' framework (Table 3.7). A total of 1214 contributory factors were identified within the 75 cases with the mean number of 17 contributory factors per case (range: 4-32 factors).

The factors fell into eight of the categories within the NPSA framework (Figure 3.21). The distribution of all the root causes is illustrated in Table 3.7. Patient related root causes were highlighted in 31.5% of cases which include clinical condition, social factors, physical factors, culture, language, mental health/psychological factors, or interpersonal relationships. In all cases the severity of the clinical condition contributed to the outcome, which reflects that amputation secondary to diabetes-related foot disease is the outcome of end stage disease. At admission, 34 of the 72 patients (47.2%) had a documented recent acute illness unrelated to diabetes-related foot disease, indicating the frailty of the cohort. Most of the clinical condition and physical factors were beyond the control of the patient and related to natural disease progression, such as sepsis at presentation, or ageing. Management prior to the amputation admission could have prevented the severity at presentation in many of the cases, therefore they were determined to be influencing factors on amputation outcome. The cases where patient compliance was a factor, such as refusal of admission or antibiotics, were determined as casual factors in the outcome. These outcomes may have been changed with better interpersonal relationships, health education and trust of the service and the effect of communication was determined to be an influencing factor in 31 cases.

Figure 3.21. Percentage of 1214 contributory factors identified in each framework category



The next largest category was organisational factors, accounting for 20% of the root causes identified. Issues with the organisational structure not being conducive to discussion and problem sharing, and professional isolation, were highlighted in 60% of cases. This was apparent across both primary and secondary care and often occurred in combination with poor communication, which was identified as a root cause in 16% of cases. GP's noted discharge summaries were either not available or contained little or no information. There was often miscommunication between specialties. In one case, diabetes care for the patient was presumed to be performed by secondary care team, when the patient was receiving endocrinology review for another comorbidity and diabetes annual review was not performed for several years. Isolated working was often an influencing factor, despite most patients reporting poor diabetes control at presentation only 20 patients were seen by diabetes specialist nurse (DSN) or a diabetologist through their admission (28%) with only 2 patients (3%) patients receiving regular review during the inpatient amputation admission.

As discussed above lack of follow up was highlighted in a large number of cases. The root cause of this issue was identified as a lack of cross speciality and combined thinking, isolated working, an unclear referral system and a lack of clear guidelines.

A lack of clear guidelines, procedures and practices was identified as a root cause in 72% of cases. This was identified as an influencing factor in most of the delayed referrals and misdiagnosis. Many GP's noted that, although there has been improvement in recent years, the process by which they access secondary care and podiatry was unclear. A lack of standardisation of care was reflected in the variance between GP practices in number of patients requiring amputation. The distribution of patients receiving amputations within the individual practices was skewed with 37 practices having 1 patient who received amputation, 14 practices having 2, 14 having 3 and 1 having 4.

Root causes related to education and training factors were identified in 5% of cases. They were an influencing factor in some cases, for example no admission notes showed clear documentation of a SINBAD score and a Waterlow score was only documented in 12. This contributed to the delayed referral between primary and secondary care and to and from podiatry. It was determined to be a casual factor in a number of cases; where there was a missed diagnosis of acute limb ischemia, a delayed diagnosis of acute limb ischaemia, delayed referral from cardiothoracic and podiatry to the vascular team and delays in senior review.

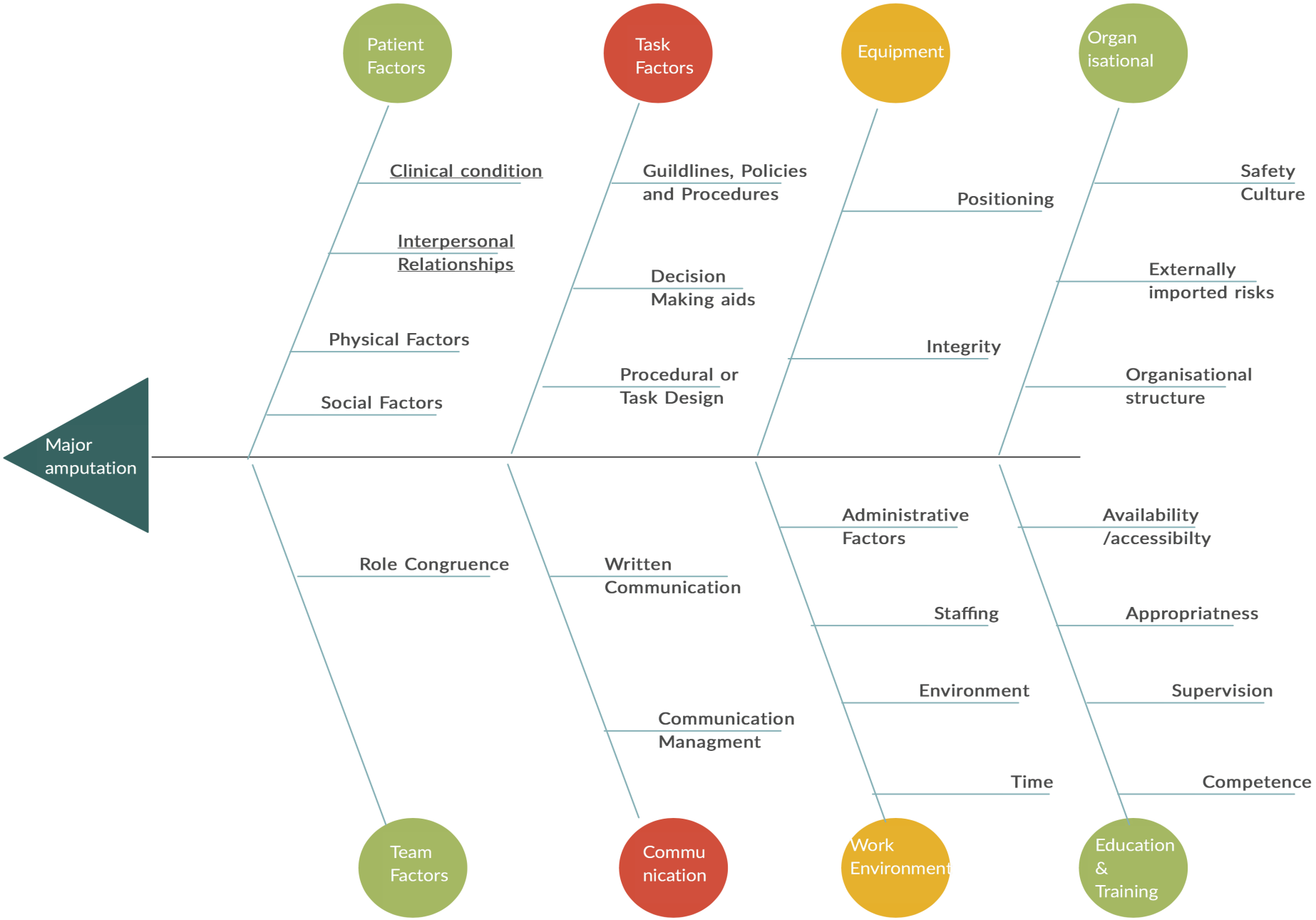
A fishbones diagram was then created to help visualise key issues and aid the final discussion (Figure 3.22)

Table 3.7: Contributory factors identified in RCA cases within NPSA framework

		Components	No.	%
Patient factors	Clinical condition	Pre-existing co-morbidity	72	100
		Complexity of condition	71	98
		Seriousness of condition	70	97
		Limited options available to treat condition	15	20
		Disability	25	34
	Physical Factors	Poor general physical state	35	48
		Age related issues	36	50
		Obese	18	25
	Social Factors	Lifestyle (smoking/ drinking/ drugs/diet)	18	25
		Life events	3	4
		Lack of support networks / social protective factors	1	1
	Mental/	Motivation issue	7	9
	Psychological Factors	Stress / Trauma	2	2
		Existing mental health disorder	2	2
		Lack of intent (Mental Health Services)	1	1
		Lack of mental capacity	3	4
		Learning Disability	3	4
	Interpersonal relationships	Poor patient engagement with services	31	43
Task Factors	Guidelines, policies and procedures	Not up to date	50	69
		Unavailable at appropriate location	52	72
	Decision making aids	Aids not available (checklist/risk assessment)	15	21
		Incomplete information (test results, patient history)	4	6
	Procedural/Task Design	Inappropriate transfer of processes from other situations	16	22
Communication	Written communication	All relevant records not stored together and accessible when required	2	3
		Records incomplete or not contemporaneous	3	4
		Written information not circulated to all team members	6	8
		Lack of information to patients	4	6
		Lack of effective communication to staff of risks (Alerts systems etc)	23	32
	Communication Management	Communication strategy and policy not defined /documented	14	19
			12	17

		Ineffective involvement of patient/carer in treatment & decisions		
		Lack of effective communication to patients/relatives of risks	26	36
		Ineffective communication flow to staff up, down and across	39	54
		Ineffective interface for communicating with other agencies	33	46
		Lack of measures for monitoring communication	33	46
Equipment	Integrity	Poor working order	2	3
	Positioning	Insufficient equipment / emergency backup equipment	2	3
Work environment	Administrative factors	Unreliable or ineffective general administrative systems	17	24
		Unreliable or ineffective administrative support	3	4
	Environment	Facility not available (failure or lack of capacity)	6	8
	Staffing	Inappropriate skill mix	6	8
		Low staff to patient ratio	5	7
	Time	Delays caused by system failure or design	27	38
		Time pressure	3	4
Organisational	Organisational structure	Hierarchical structure/Governance structure not conducive to discussion, problem sharing, etc.	43	60
		Professional isolation	43	60
	Externally imported tasks	Lack of service provision	9	13
	Safety culture	Inappropriate safety / efficiency balance	43	60
		Lack of risk management plans	51	71
		Acceptance/toleration of inadequate adherence to current practice	51	71
Education and training	Competence	Lack of knowledge	22	31
		Lack of skills	10	14
		Inexperience	11	15
		Inappropriate experience or lack of quality experience	5	7
		Unfamiliar task	1	1
		Lack of testing and assessment	4	6
	Supervision	Inadequate supervision	4	6
		Lack of / inadequate mentorship	1	1
Team Factors	Role Congruence	Lack of shared understanding	53	74
		Role + responsibility definitions misunderstood/not clearly defined	47	65

Figure 3.22. Fishbone diagram of main contributory factors identified in the RCA



3.5 Discussion

The current study is the first to systematically investigate the root causes of amputations secondary to diabetes-related foot disease within a Welsh health board. The most important finding from the study was almost all of the amputations were determined potentially preventable. The greatest contributory factors were patients' clinical condition at time of presentation. This was affected by the disease length and patient adherence to treatment as well as by the treatment received in primary and secondary care prior to the referral and at time of referral. In many cases the causes were found to be disease related which was to be expected as amputation often occurs as the end event of a long disease process. Around 80% of amputations are believed to be preventable (NICE, 2016) and many of the root causes in the review related to an acceptance within the clinical environment that amputation was inevitable.

Peripheral vascular disease was the cause of amputation in 83% of cases. Achieving successful outcomes for these patients requires more than adequate surgical intervention (NICE, 2018). In a prospective study of over 600 patients with severe PVD developing foot ulcer who were unable to receive a reperfusion procedure almost 50% achieved ulcer healing without amputation due to adequate medical intervention and review (Forsythe et al., 2015). For the cases reviewed within this RCA where revascularisation was not possible the patients were discharged from secondary care or lost to follow up and then re-presented at the point where the only option was amputation. Monitoring and medical management is required for these patients, which did not occur. More input is required if amputation is to be prevented. However, the RCA only identified those patients that went on to undergo amputation, it may be that those patients that did not progress to amputation were receiving follow up.

All of the patients in the review were high-risk according to NICE guidelines, therefore at an increased risk of developing foot ulceration increasing the risk of progress to amputation(Diabetes UK, 2015c). Although amputation was deemed necessary at the time of procedure to save life, in most cases intervention prior to this point may have, or would have prevented the outcome. The International Working Group on the Diabetes Foot recommend

patients with ulceration secondary to diabetes foot disease should be treated with medical urgency (Schaper et al., 2012) but many patients had long delays in their care pathway and many were not receiving ongoing secondary care despite remaining in the high foot risk category.

A lack of guidelines, policies and procedures were identified as a contributory factor in 72% of cases. This was reflected by the GP comments regarding unclear referral pathways. A solution to this would be a clear and standardised referral pathway for the management of diabetes-related foot disease from primary to secondary care and within secondary care for patients. This would also address the issue of poor communication up, down and across, highlighted as a contributory factor in 54% of cases and would offer a solution to the lack of monitoring of this communication. Other major contributory factors were acceptance of the current standards across primary and secondary care and a lack of management of the patients between settings with a lack of shared understanding as reflected by the large number of delays or loss to follow up. Only with a shared organisational responsibility can we hope to achieve the change required to improve patient care and ultimately reduce our amputation rate.

A multidisciplinary foot care team is suggested as a basic requirement for quality care of the diabetes foot by both NICE and Diabetes UK (NICE, 2016). Units with a formal MDT in place have been shown to have favourable amputation rates(Holstein et al., 2000; Krishnan et al., 2008; Schofield et al., 2009). This was demonstrated definitively in the South West of England following a peer review of services after introduction of service provision in 10 key areas(R. B. Paisey et al., 2018a) (Table 3.8). Marked reduction in amputation rates were demonstrated in all CCGs that undertook the recommendations, with no change in amputation rate seen in those that did not implement a MDT. The region had similar amputation rates prior to RCA to those seen within ABMU, providing a strong rationale for the introduction of a MDT. Furthermore, treatment plans decided within a MDT for high risk patients have been shown to reduce major amputation rates (Forsythe et al., 2015). For change to be monitored, prospective review is required and this has been shown to improve outcomes in other medical fields following RCA (Perkins et al., 2005a) as well as for major amputation (R. B. Paisey et al.,

2018a). An MDT would provide an opportunity to develop a prospective review of services as all patients would be managed within the same pathway. In our aggregate analysis is was not possible to review near misses as this would require identification and review of all admissions for foot disease regardless of whether the patient progressed to amputation. Retrospectively this would be heavily time extensive. A MDT with adequate prospective records of patients with diabetes foot disease would make this possible and add to the strength of future analysis.

Table 3.8. Commissioning recommendation for effective care of diabetes foot disease in the Southwest review (R. B. Paisey et al., 2018a)

Commissioning recommendations
1. Patient education at annual review
2. Regular community healthcare professional education
3. Adequate podiatry community staffing with rotation in to MDFT
4. Job planned MDFT weekly
5. Administrative support
6. Pathways and communication of plan of care to patient
7. Identification of diabetes in-patients and their foot checks
8. Orthotist an integral part of MDFT
9. Urgent vascular opinion available to foot clinic staff
10. Ulcer database and root cause analysis of all amputations

MDFT; Multidisciplinary foot team

The commissioning recommendations in the South West review address may of the areas of issue highlighted within the current RCA. We are at the beginning stages of addressing some of the issues raised since 2015-2016 but further progress is needed. The number of amputations from the RCA were in keeping with the national vascular registry audit. Reviewing amputation numbers within the audit in the succeeding years show that high amputation rates in ABMU have continued since the review (National Vascular Registry, 2018).

Although ABMU is not completely comparable to the South West region, the commissioning recommendations could act as a guideline to direct resources and funding as they have been proven to be effective. Sheffield CCG implemented a similar RCA in 2007 (Diabetes UK, 2015a). Their findings were similar, suggesting that poor primary to secondary care links and a lack of a secondary care MDT were contributory factors to their high amputation rates. To address this, they implemented a diabetes foot hotline, single point of referral for all diabetes foot problems, better training for primary care and a more comprehensive MDT. After implementing these changes, total amputation rates reduced from 4.4 per 1000 people with diabetes in 2007-2010 to 2.7 per 1000 (45% in 3 years) and had a reduction in major amputations from 1.75 to 0.9 per 1000 people with diabetes, supporting the view that a large proportion of amputations are preventable. The estimated annual financial savings for the CCG were at least £300,000 and patient satisfaction with the service was above 90%.

3.5.1 Recommendations

Based on the root causes identified and the outcomes of RCA in other health boards the following recommendations were made in a report presented to the health board vascular commissioning group.

1. The introduction of a primary and secondary care pathway for care of diabetes-related foot disease to ensure a clear referral pathway. The aim of the pathway would be to improve communication of the route to access care for all patients and professionals within the pathway and to ensure effective follow up and management plans across care settings. This would aim to address the issues of poor communication, loss and lack of follow up and team factors.

2. Facilitate a Multidisciplinary Foot Care Team as recommended by NICE and Diabetes UK. This will require support and job planned time from each of the recommended specialty staff. To meet gold standard care, the MDT would comprise of vascular and orthopedic surgeons, diabetologists, podiatry, radiology and microbiology. Meetings would occur on at least a monthly basis and the team should be aware of high and active risk patients.

3. Improved access to vascular services to facilitate prompt review of all urgent referrals both as inpatient and outpatient.

4. Appropriate support from imaging services for at risk patients including improved access to inpatient MRI.

5. The continued education of patients and staff to ensure best practice and improved standards of care including continued pressure from the Think Glucose Group and use of educational resources such as Pocket Medic - a video-based patient educational tool already utilised by diabetes services in the health board.

6. A lobby for increased Public health awareness of diabetes and its complications including importance of foot health.

7. An independent external review of current practice to identify further areas for improvement by the national vascular society.

8. Finally, continued engagement with primary and community care to establish cohesive working relationship supported by ongoing engagement between primary and secondary care through teaching days.

3.6 Summary and Limitations

The observations from this RCA identified a number of areas in which resources could be directed which may reduce the rate of amputation within ABMU. Unlike in engineering where a RCA cycle ends with testing and conformation of root cause this is often not possible in a health care environment. The amputation rate within ABMU will be the outcome measure but until changes are implemented and time has passed it is not possible to determine whether the causes identified where accountable for the amputation rate. This could take several years since, as discussed previously, amputation is the end stage of a long disease process.

3.6.1 Clinical significance

As discussed previously the effect of implementing the results of a RCA for this topic have been found to produce measurable effect in amputation reduction. The RCA has been presented to the health board through a vascular steering group and the health board is currently looking into piloting a multi-disciplinary clinic on one site, as well as piloting a telemedicine service in one of the hospitals within the trust (Appendix VI).

3.6.2 Limitations

As noted above, for some cases notes were missing and it was not possible to access GP or podiatry data for all cases. It is possible that a root cause present within these notes may have been missed or the issues found within the review may have been greater than presented. During the review process an obstacle was found in healthcare stakeholder availability; not all members of the recommended RCA team were available to assist in the review. Although most members of the recommended team were available for part of the analysis, the analysis was heavily reliant on work done by the orthopaedic team and myself that may have introduced bias in interpretation of the findings. As there is tendency for analysts to have a sensitivity to the topics most pertinent to their own professional community (Rasmussen, 1990), the causes identified by the analyst determine the generation of recommendations (Woodcock, 1995).

As the analysis happened after the event, many of the patients were deceased, staff had moved hospital and it was often unclear who the treating physician and nursing staff where, it was not possible to obtain face to face interviews. Although the events of the incident were adequately analysed, a large part of the original analysis from the NPSA was focused on staff and patient psychological factors which could not be assessed and may have had some impact of the events analysed in the RCA.

Retrospective analysis, especially aggregate root cause is susceptible to hindsight bias and negative judgment of the event because of its negative outcome (Slakey, Simms, Rennie, Garstka, & Korndorffer, 2014). Knowledge of an outcome by those assessing events that have occurred results in a predilection to overestimate how predictable an outcome would have seemed to those involved at the time of the event (Durso et al., 1999). Although attempts were made to avoid this by using approved frameworks, CED analysis and reviewers across specialities, it is not possible to ascertain how much effect this would have on the final report. The use of the fishbone diagram for the review has some reported disadvantages. It requires a detailed knowledge of the problem, this was not a limitation in this review as there was a senior review team, but it is tends to emphasise opinions and overlook casual interactions in the root cause analysis (Bhote, 1988.) and it only identifies potential causes (Sproull, 2001).

Many different approaches can be taken to undertake an investigation of an adverse incident. A number of models have been created to make investigations more subjective, one of which is RCA. There has been some criticism of the RCA approach as it is based on a linear chain of event accident causation model (Hollnagel, 2004). It is argued that this is not appropriate within a health care setting as incidents often occur within a complex system. The main criticism of this approach is the lack of consideration of organisational and technical aspects (Hollnagel, 2004; Lundberg et al., 2009). The approach undertaken within this study was that recommended by Diabetes UK (2017) and organisational and technical aspects were addressed by utilising the NPSA contributory factors framework. Despite this, it is not possible to say that another approach may have resulted in different findings.

CHAPTER FOUR

Social and clinical risk factors contributing to the risk of amputation in persons with diabetes referred to Secondary care services in the Swansea locality

4.1 Introduction

Most health inequalities can be ascribed to variation in either the demographic or risk factor profile of a population, along with their access to services. Within the previous chapter inequalities in the provision of care were explored with respect to diabetes-related major amputations. Policies that seek to improve health outcomes need to address social determinants of health in addition to biological and lifestyle factors. It is important to explore the social determinants and biological factors associated with amputation risk along with the current service provision that may contribute to the amputation rate inequalities within the specific population of ABMU.

It is accepted that for many non-communicable diseases, that the prevalence of disease is higher in socio-economically deprived patient groups (Stringhini et al., 2011). It is postulated that those from deprived populations are less likely to adopt healthy behaviours and therefore have higher rates of obesity and smoking (Stringhini et al., 2011). A 2015 health determinants for Wales study produced by the Public Health Wales Observatory (2018), using World Health Survey data, reported smoking amongst adults was 2.4 times higher in the most deprived fifth of the Welsh population when compared to the least deprived fifth. The report also found that 63.1% of people in the most deprived fifth of the Welsh population were overweight compared to 53.2% in the least deprived, with the disparity increasing over time (Public Health Wales Observatory, 2018). Although links between socioeconomic status cardiovascular outcomes and T2DM risk have been established (Psaltopoulou et al., 2017) currently there has been little investigation into the link between socioeconomic deprivation and the incidence of lower limb amputation secondary to diabetic foot disease within UK populations.

There is considerable variance in the rate of amputation in persons with diabetes and in the prevalence of risk factors in these patients between countries and within populations (Naseer Ahmad et al., 2014; Chaturvedi et al., 2001; P. W. Moxey et al., 2011a). Studies have demonstrated, as with many other chronic diseases, there is an increase in the prevalence of T2DM in those with lower socioeconomic status (Connolly, Unwin, Sherriff, Bilous, & Kelly,

2000) along with an increase in other diabetes-related complications such as retinopathy in T1DM (Low et al., 2015). It is unclear, whether socioeconomic status contributes the variance in amputation rates between populations as the available literature is unclear.

A recent study from Dundee described that those from the most deprived social quintile in Scotland had a 1.7 times increased risk of foot ulceration (Leese et al., 2013). A lower socioeconomic status has also been demonstrated as a risk factor for PVD (S. Arya et al., 2018). Ahmad et al (2014) described a positive association between social deprivation and amputation rate in PVD, with a greater number of amputations performed in the most deprived areas of England, although this association was not statistically significant. In larger population-based studies using hospital discharge data it is hard to explore person and limb related risk factors due to inconsistency in the coding for routine clinical data such as BMI, blood pressure, foot risk and smoking status, limiting its use. As BMI and smoking status are thought to explain part of the inequalities in health outcomes driven by social deprivation and also are known risk factors for amputation it is important to investigate their presence and risk within the population of ABMU. By utilising a hospital-based population with access to clinic letters and hospital notes these measurements can be accurately obtained. This chapter addresses the burden of smoking, history of foot risk and other clinical variables such as systolic blood pressure, and BMI that are not coded well within healthcare data but are known to be associated with amputation (Hippisley-Cox & Coupland, 2015a).

The rates of amputation vary by geographical areas (NICE, 2016), from country to country and within regions of the UK (Edward J. Boyko et al., 2018). Swansea has consistently had a greater percentage of people living in material deprivation than the average for Wales over the last 5 years (StatsWales, 2019). As funding for the NHS becomes more limited nationally and prudent healthcare becomes a core tenant of NHS Wales it is pertinent to identify high-risk patient groups to allow for services to be directed to those most in need.

As discussed in the previous chapter recent NWIS data is suggestive that ABMU has a higher rate for diabetes-related amputations than other health boards within Wales (NWIS, 2017). This does not appear to be due to a higher incidence of diabetes and diabetes related foot disease (R. Thomas et al., 2010b), and it is unclear whether this is due alone to the access or level of care patients are receiving. The RCA highlighted that all patients had comorbid conditions at the time of amputation and complexity of condition played a role in 98% of major amputation cases explored. Within the RCA it was not possible to accurately assess the effect of social deprivation or compare the characteristics between those who did and did not undergo amputation. With variance in risk factors found between populations (Naseer Ahmad et al., 2014) and with exploration of risk factors for amputation not previously performed within Wales, it was important to explore risk factors within this specific population. Highlighting high risk patient groups to direct preventative health care interventions can play a role in developing cost-effective evidence-based solutions to the growing issue.

4.2 Hypothesis and Aims

Within the Swansea locality, my hypothesis was that the risk of lower limb amputation would not be significantly associated with socio-economic status, BMI or smoking status in people with diabetes attending secondary care (hospital) services.

The specific aims of this chapter are:-

(i) To identify if socio-economic status, BMI or smoking status is associated with diabetes-related lower limb amputation in a secondary care population when controlling for other clinical and biochemical risk factors for amputation.

(ii) To identify the effect of amputation on survival versus the baseline secondary care population when controlling for other risk factors for mortality.

4.3 Methods

4.3.1 Study design

The study used a retrospective observational cohort design, which linked data from diabetes outpatient annual reviews and an amputation dataset derived from NWIS data. This allowed a cohort of patients to be followed over a period of time. The study was approved as a service-based evaluation by the clinical director (appendix I).

4.3.2 Participants

The study population were patients aged 18 years and over attending secondary care diabetes clinics in Morriston Hospital during the period of the 1st January 2006 to 31st December 2010; a total of 2024 people. Subjects may have attended once or on up to four occasions over the period and had initial contact with the service at any time prior to or during this period. The date of the first clinic attendance in the period between 1st January 2006 and 31st December 2010 was taken as the entry date into the study. The cohort included people with a diagnosis of T1DM or a diagnosis of T2DM with either an insulin requirement, poor glycaemic control not managed in primary care, complex needs or associated marco- or microvascular complications from their diabetes. People with a documented history of amputation within the clinic notes prior to 2006, attending clinic for another endocrine disorder, not attending for diabetes review or with home postcodes from outside the health board were excluded from the study. Data on ethnicity were not available.

All data from the diabetes annual review is recorded directly onto the clinical electronic database (Leicester Clinical Workstation). The database contains routinely collected diabetes related data including data from an annual foot assessment performed by a podiatrist as detailed in a previous publication (R. Thomas et al., 2010b). Demographic data recorded included gender, age, postcode, first and last clinic attendance, diabetes type, length of diagnosis and smoking status. Clinical markers recorded in clinic attendance are; BMI, Systolic (SBP) and diastolic blood pressure (DBP), HbA1c, serum creatinine, serum total cholesterol, history of PVD, history of neuropathy and foot risk including a history of previous amputation.

Foot risk was classified as low, medium, high and ulcerated/active as described using the framework by NICE and Diabetes UK (Diabetes UK, 2015c; NICE, 2016). Neuropathy was determined in the clinic visits by lack of 10g monofilament sensation and PVD was determined using ankle brachial pressure index (ABPI) or toe brachial pressure index (TBPI) testing of each limb.

4.3.3 Socioeconomic deprivation

In addition to the data from the initial data sets, patient post code was used to calculate a deprivation score for each individual using the Welsh Index of Multiple Deprivation (WIMD) (StatsWales, 2014). The WIMD is a measure of socioeconomic status based on place of residence. It combines information from several different indicators of deprivation, allowing different weights for each, to create a single figure to represent the level of deprivation. WIMD scores are calculated for the 1909 lower super output areas (LSOA) in Wales. LSOA areas are homogenous areas of equal size with an average population of 1600 people. Those with the lowest combined WIMD score are the most deprived and vice versa. The WIMD score is split into quintiles from the most to the least deprived groups.

4.3.4 Non-socioeconomic deprivation variables

Other variables were included which may confound or control the effect of socioeconomic deprivation on diabetes-related amputation, shown in Table 4.1.

Table 4.1 Non-socioeconomic deprivation variables included in database analysis

Demographic variables	Clinical variables	Biochemical variables
Age	Diabetes Type	Mean Arterial Pressure
Gender	Diabetes Duration	Systolic Blood Pressure
	Smoking Status	Diastolic Blood Pressure
	Foot risk	Creatinine
	History of Neuropathy	Total Cholesterol
	History of PVD	HbA1c
	Body Mass Index	

PVD: Peripheral Vascular Disease; HbA1c: Haemoglobin A1c

For BMI and biochemical variables, an average of the clinic visits prior to end of study or amputation was taken to give an idea of health over the study period. BMI is presented in categories; underweight range <18.5 kg/m^2, normal weight range 18.5-24.9 kg/m^2, overweight 25.0-29.9 kg/m^2 and overweight 30+ kg/m^2 as per NHS guidelines (NHS, 2019). For age, postcode, smoking status and foot risk the information from the last visit prior to amputation or end of study were used. Time from birth and diagnosis of diabetes to date of initial amputation was used for calculations of age and length of diabetes respectively. If no amputation was performed, then time from birth and diagnosis of diabetes to end of study or date of death was used if it was prior to the end of the study period.

4.3.5 Follow-up & Outcomes

The clinic data were collated with NWIS data, a database from the health boards central informatics team of all patients undergoing amputation between 1st January 2006 to 31st December 2015. The databases were linked using anonymised patient identifiers. The NWIS database included information on age at amputation, operation performed and date of operation, any subsequent amputations on the same admission, length of stay and mortality data. The data are generated from hospital coding at the time of discharge of each admission event. Lower extremity amputation is defined as above knee, below knee, through ankle, forefoot or toe within the database. The level of amputation, age of amputation, number of amputations and mortality were noted.

Patients were followed from the date of first clinic to the date of first amputation. If no amputation was performed, the end of review period, 31st December 2015 or date of death was used if this was prior to the end of the study period. This gave a range of follow up from 9-3640 days. If multiple amputations occurred within the initial amputation admission, the highest level of amputation for the initial admission for amputation was identified and used. This created two cohorts of patients; those who attended the secondary care clinic who had proceeded to amputation and those who had not.

4.3.6 Statistical analysis

Statistical analysis was performed using R (R version 3.6.1 2019) and figures were produced using the package ggplot2 (Wickham, 2016). For comparison of baseline variables between cohorts, the chi-squared was used for categorical variables. Student t-test and Mann Whitney U test were used for normally and non-normally distributed continuous variables, respectively.

Binary logistic regression was used to identify predictors of amputation. The odds ratio of amputation for each variable was calculated unadjusted in a univariate model and then adjusted for other significant demographic and disease risk factors in a multivariate stepwise logistic regression model. Variables were grouped and entered in steps. The groups consisted of non-modifiable risk factors (age & gender), lifestyle risk factors (WIMD, history of smoking & BMI), clinical risk factors (length of diabetes, diabetes type, SBP & DBP), biochemical risk factors (HbA1c, creatinine & cholesterol) and limb risk factors (foot risk score and history of neuropathy or PVD). Factors were entered in a stepwise manor to find the most parsimonious model that included lifestyle risk factors. The most parsimonious model included all variables. A sensitivity analysis was run with WIMD scores as a continuous variable rather than split into quintiles. This analysis produced similar results to the primary analysis. Variables were entered into the model and Cox proportional hazard model was used to assess risk of death.

To handle missing data within variables fully conditional specification method multiple imputation was used in R (version 3.6.1) using the mice package (version 3.9.0) using 5 iterations to carry out estimation of missing values. Five copies of data were produced in the imputation process (Sterne et al., 2009). Copies were independently analysed in all statistical analyses and estimates of parameters were averaged across copies to obtain mean estimate and 95% confidence intervals.

4.4 Results

4.4.1 Participant characteristics

A total of 2024 people living within the health board attended for diabetes review over the study period. Table 4.2 shows the characteristics of the population at entry into the study. The median age of the cohort was 62 years (range: 51.5-72.5 years). Fifty seven percent (n=1155) of the cohort were men and the population was overweight with a median BMI of 30.8 kg/m^2 (range: 26.6-35.1 kg/m^2). The median duration of diabetes for the population was 6.5 years (range: 0.23-18.89 years) and 80.2% (n=1622) had T2DM. The average HbA1c of the population was elevated at 8.6 ±1.68 % (70 ±5.1 mmol/mol) and the average SBP was within the hypertensive range (140.5 ±19.21 mmHg). Fifteen percent (n=301) of patients did not have a documented foot examination within the period. 14.4% (n=292) had a history of diabetes neuropathy, 8.6% (n=174) a history of PVD and 48.7% (n=961) had ever smoked.

One hundred and seventeen (5.8%) people underwent a total of 219 amputations during the follow-up period. In total 138 minor amputations (63.0%) and 81 (37.0%) major amputations were performed. Within the period, 51.3% (n=60) had a single amputation procedure at any level, 27.4% (n=32) had 2 amputations, 12.8% (n=15) underwent three procedures and 8.5% (n=10) required 4 or more. For 74 people (63.2%) the first amputation within the period was a minor amputation and for 45 people (36.8%) the first amputation was major. Fifty-nine people (50.4%) had only a minor amputation over the period, with the highest level of operation being a toe amputation for 71.2% (n=42) and below the ankle for 28.9% (n=17). Fifty-eight people (49.6%) underwent a major amputation with the highest level of amputation received during the period being a BKA for 62% (n=36) and AKA for 38% (n=22). At the end of the study period 667 (32.9%) patients had died.

Data were complete for age, gender, type of diabetes, duration of diabetes, WIMD and history of neuropathy and PVD. The variable with the largest amount of missing data was foot risk with data missing for 14.9% of patients as they had not attended for the foot review as part of their clinic visit. There was no significant difference in amputation risk for people that did

and did not attend for a foot review, 5.3% (n=16) of people who did not attend underwent amputation compared to 5.9% (n=101) in the group that did attend (appendix III). Cholesterol data were missing for 13.0% of patients (n= 264), with a small amount of data missing for SBP & DBP (5.8%), BMI (2.0%), creatine and HBA1c (both 0.1%). In total a datapoint was missing for 22% of patients and a decision was made to use multiple imputation to handle these data points.

Table 4.2 Characteristics of all patients attending secondary care diabetes clinic

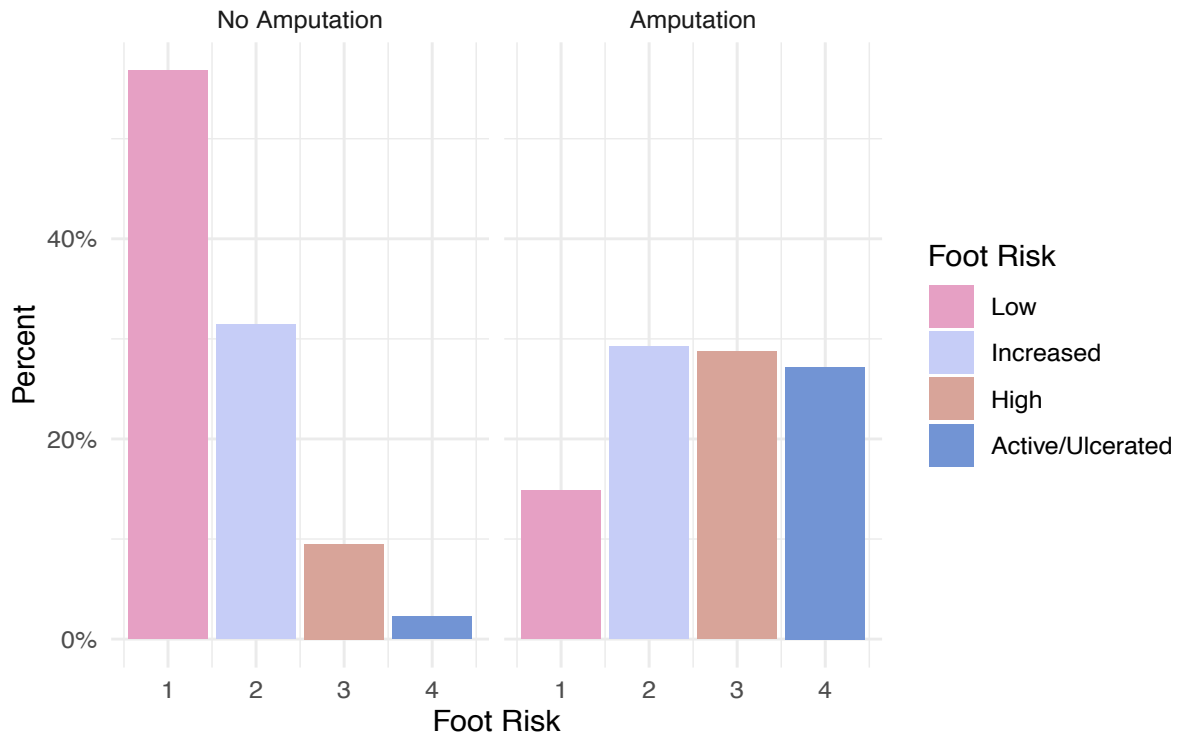
Variable		n=2024	n (%missing)
Age (years)		62 (51.5-72.5)*	2024 (0)
Gender	Women	869 (42.9%)	2024(0)
	Men	1155 (57.1%)	
Diabetes Type	T1DM	402 (19.8%)	2024(0)
	T2DM	1622 (80.2%)	
Duration Diabetes (years)		6.5 (0.23-18.89)	2024 (0)
WIMD quintile	1 - Most deprived	665 (32.9%)	2024 (0)
	2	423 (20.9%)	
	3	373 (18.4%)	
	4	255 (12.6%)	
	5 - Least deprived	308 (15.2%)	
Smoking status	Never	1010 (49.9%)	1971 (2.6)
	Ex smoker	610 (30.1%)	
	Current	351 (17.3%)	
Foot risk	Low	916 (45.3%)	1723 (14.9)
	Increased	546 (27.0%)	
	High	193 (9.5%)	
	Active/Ulcerated	68 (3.4%)	
	Not performed	301 (14.9%)	
History of Neuropathy	Present	292 (14.4%)	2024 (0)
	Absent	1732 (85.6%)	
History of PVD	Present	174 (8.6%)	2024 (0)
	Absent	1850 (91.4%)	
BMI (kg/m^2)		30.8 (26.6-35.1)*	1984 (2.0)
SBP (mmHg)		140.5 ±19.21^X	1907 (5.8)
DBP (mmHg)		78.3 ±9.62^X	1907 (5.8)
Creatinine (umol/L)		82.8 (66.0-99.7)*	2021 (0.1)
Total cholesterol (mmol/L)		4.4 ± 1^X	1760 (13.0)
HbA1c (%)		8.6 ±1.68^X	2022 (0.1)
HbA1c (mmol/mol)		70.5 ±6.6^X	

Data are presented as count (%) *Data are presented as median and IQR XData are presented as mean and standard deviation. T1DM: Type 1 Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus; WIMD: Welsh Index of Multiple Deprivation; PVD: Peripheral vascular disease; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HbA1c: haemoglobin A1c.

4.4.2 Univariate analysis

Table 4.3 shows the baseline characteristics of the amputation and non-amputation groups after imputation of missing data. In the group that underwent amputation there was a greater proportion of men (p=0.002) and a greater number of people in the higher foot risk categories (p<0.001) (Figure 4.1). There were more people with a history of neuropathy (p<0.001) and PVD (p<0.001). The people in the amputation group had significantly higher mean systolic BP (p<0.001), HbA1c (p=0.02), and a significantly lower mean total cholesterol (p=0.04). The median creatinine was also significantly higher (p<0.001). More patients in the amputation group had a history of smoking compared to the group that did not progress to amputation (50.4% vs 48.9% respectively) but this did not reach statistical significance (p=0.39). Age, diabetes type, diabetes duration, BMI and diastolic blood pressure showed no statistical difference between groups.

Figure 4.1: Percentage of total cases in each foot risk category by amputation status



Chi squared analysis revealed a significant difference in distribution of amputation between foot risk groups (p=<0.001).

Table 4.3 Baseline characteristics between Amputation and Non-amputation groups.

	Amputation	Non-amputation	P value
n (%)	117 (5.8%)	1907 (94.2%)	
Age (years)	61.3 (52.8-69.8)	60.2 (49.7-70.7)	0.39
Men	83 (70.9%)	1072 (56.2%)	**0.002**
T2DM	92 (78.6%)	1530 (80.3%)	0.67
Duration Diabetes (years)	9.27 (2.2-16.3)	6.32 (0.1-12.5)	**0.003**
WIMD			0.29
1	46 (39.3%)	619 (32.5%)	
2	28 (23.9%)	395 (20.7%)	
3	19 (16.2%)	354 (18.6%)	
4	12 (10.3%)	243 (12.7%)	
5	12 (10.3%)	296 (15.5%)	
Smoking status			0.39
Never smoked	58 (49.6%)	974 (51.1%)	
Ever smoked	59 (50.4%)	924 (48.9%)	
Foot risk			**<0.001**
Low	17 (14.5%)	1083 (56.8%)	
Increased	34 (29.1%)	599 (31.4%)	
High	34 (29.1%)	181 (9.5%)	
Active/Ulcerated	32 (27.3%)	44 (2.3%)	
Neuropathy	43 (36.8%)	249 (13.1%)	**<0.001**
PVD	33 (28.2%)	141 (7.4%)	**<0.001**
BMI (kg/m^2)			0.28
Underweight	2 (1.7%)	7 (0.4%)	
Average	15 (12.8%)	276 (14.5%)	
Overweight	38 (32.5%)	544 (28.5%)	
Obese	62 (53.0%)	1071 (56.2%)	
SBP (mmHg)	147.8 ±23	140.1 ±18.9	**<0.001**
DBP (mmHg)	78.3 ±11.1	78.3 ±9.5	0.92
Creatinine (µmol/L)	97 (71.0-123.0)	82 (66.1-97.9)	**<0.001**
Total Cholesterol (mmol/L)	4.15 ±1	4.36 ±1	**0.04**
HbA1c (%)	9.07 ±2.11	8.59 ±1.65	**0.02**
HbA1c (mmol/mol)	75.6 ±11.3	70.4 ±6.5	

T2DM: Type 2 diabetes mellitus; WIMD, Welsh Index of Multiple Deprivation; PVD, Peripheral vascular disease; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HbA1c, haemoglobin A1c

The unadjusted odds ratio for all characteristics are shown in Table 4.4. When looking specifically at the main endpoints, univariate logistic regression analysis showed that those in any quintile less deprived than the most deprived quintile were less likely to undergo amputation. In the least deprived quintiles patients had almost half the probability of undergoing an amputation (odds ratio (OR) 0.54 [0.28-1.05], p=0.06) However, the risk reduction was not statistically significant for any quintile.

Risk factors that increased the odds of amputation included: male gender (OR 1.9 [1.26-2.86], p=0.002); history of neuropathy (OR 3.87 [2.60-5.77], p<0.001); history of PVD (OR 2.12 [3.18-7.62], p<0.001); SBP (OR 1.02 per 1mmHg increase [1.01-1.02], p<0.001); creatinine (OR 1.01 per 1 µmol/L increase [1.00-1.01], p<0.001); and HbA1c (OR 1.17 per 1% increase [1.05-1.29], p=0.003). All categories of foot disease increased the odds of amputation compared to low risk. Patients within the active risk/ulceration foot risk category had an odds ratio of 50.9 (p<0.001). Increasing total cholesterol reduced the odds of amputation (OR 0.81 per point increase [0.65-0.99], p=0.05).

Table 4.4 Odds ratios unadjusted and adjusted for covariates for lower limb amputations in a secondary care population with diabetes

		OR (95% CI) Unadjusted	p value	OR (95% CI) Adjusted	P value
Age		1.01 (0.99-1.02)	0.42	0.97 (0.95-1.01)	0.26
Gender	Women	ref		ref	
	Men	1.90 (1.26-2.86)	0.002	1.80 (1.05-3.09)	**0.03**
Diabetes type	T1DM	ref		ref	
	T2DM	0.91 (0.58-1.4)	0.67	0.77 (0.35-1.72)	0.56
Duration of diabetes		1.00 (1.00-1.00)	0.002	1.00 (1.00-1.00)	0.70
WIMD	1	ref		ref	
	2	0.95 (0.59-1.56)	0.85	1.10 (0.57-2.11)	0.79
	3	0.72 (0.42-1.25)	0.25	0.99 (0.48-2.03)	0.97
	4	0.66 (0.35-1.28)	0.22	0.73 (0.33-1.60)	0.43
	5	0.55 (0.28-1.05)	0.07	0.74 (0.34-1.61)	0.45
Smoking	Never	ref		ref	
	Ever	1.07 (0.74-1.56)	0.71	0.73 (0.44-1.20)	0.22
Foot risk	Low	ref			
	Increased	3.35 (1.74-6.45)	<0.001	3.48 (1.65-7.32)	**<0.001**
	High	11.9 (6.16-22.86)	<0.001	7.94(3.58-17.6)	**<0.001**
	Active/Ulcerated	50.9 (24.93-103.8)	<0.001	47.6 (18.9-119.6)	**<0.001**
Neuropathy	Absent	ref		ref	
	Present	3.87 (2.60-5.57)	<0.001	1.59 (0.93-2.72)	0.08
PVD	Absent	ref		ref	
	Present	4.92 (3.18-7.63)	<0.001	2.12 (1.18-3.82)	**0.01**
BMI	Normal weight	ref		ref	
	Underweight	5.14 (0.98-26.9)	0.05	2.50 (0.07-84.95)	0.07
	Overweight	1.28 (0.69-2.38)	0.43	1.36 (0.58-3.17)	0.58
	Obese	1.03 (0.74-1.56)	0.92	0.92 (0.39-2.16)	0.39
SBP	(mmHg)	1.02 (1.01-1.03)	<0.001	1.03 (1.02-1.05)	**<0.001**
DBP	(mmHg)	1.00 (0.98-1.02)	0.91	0.99 (0.96-1.03)	0.59
Creatinine	(umol/l)	1.01 (1.00-1.01)	<0.001	1.00 (1.00-1.00)	0.26
Total Cholesterol)	(mmol/L)	0.81 (0.65-0.99)	0.05	0.82 (0.61-1.09)	0.17
HbA1c	(%)	1.17 (1.05-1.29)	0.003	1.26 (1.09-1.46)	**0.002**

Data is presented as odds ratio (95% CI interval). Unadjusted OR are the results from univariate analysis, WIMD, Welsh Index of Multiple Deprivation; PVD, Peripheral vascular disease; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HbA1c, haemoglobin A1c.

4.4.3 Multivariate analysis

There was no significant difference in the likelihood of amputation during the follow-up for patients in the most deprived quintile compared to the least deprived (OR 0.73 [0.34-1.61], p=0.045), having adjusted for the effects of non-modifiable risk factors (age & gender), other lifestyle risk factors (history of smoking & BMI), clinical risk factors (length of diabetes, diabetes type, SBP & DBP), biochemical risk factors (HbA1c, creatinine & cholesterol) and limb risk factors (foot risk score and history of neuropathy or PVD) (Table 4.4).

Following adjustment for co-variates, all significant factors from the univariate analysis were predictive of amputation excluding cholesterol (OR 0.82 [0.61-1.09], p=0.18), creatinine (OR 1.00 [1.00-1.00], p=0.26) and neuropathy (OR 1.59 [0.93-2.72], p=0.09). Although the effect of the variables remained in the same direction, they each lost statistical significance. Compared to women, men were significantly more likely to undergo amputation (OR 1.80 [1.05-3.09], p=0.03). A history of PVD (OR 2.12 [1.18-3.82], p=0.01), increasing systolic blood pressure (OR 1.03 per 1mmHg increase [1.02-1.05], p<0.001) and increasing HbA1c (OR 1.25 per 1% increase [1.09-1.46], p=0.002) were all positively associated with risk of amputation. Increasing foot risk showed a very strong association with increasing likelihood of amputation. All categories of foot risk had a positive association with the risk of amputation compared to the cohort in the low-risk category, with the odds ratio for active/ulcerated group attenuated but still substantial at 47.55 ([18.91-119.56], p<0.001).

4.4.4 Survival following amputation

The prevalence of mortality was 32.9% in the follow-up period. Variation in baseline characteristics between the cohort that survived and those that did not are shown in Table 4.5. There was a significant difference in mortality between the amputation and non-amputation group, 47% (n=55) of patients who received amputation died compared to 32% (n=612) of patients who did not (p=0.001). Patients who died were significantly older; mean age 55.2 ±14.2 years in patients who lived vs 70.4 ±10.8 years in those that died (p<0.001), were more likely to be diagnosed with T2DM, had a longer duration of diabetes and a greater proportion had a higher foot risk score. Of those patients receiving amputation, 1-year mortality was 20.5% and 5-year mortality was 42.7%.

There was a significant difference in mortality between those who had amputation and those who did not, with those undergoing amputation significantly more likely to die at any time during the follow-up period (HR 7.31 [5.37-9.95] p <0.001). Having adjusted for the effects of age, duration of diabetes, foot risk, history of neuropathy and PVD, BMI, DBP and total cholesterol the likelihood of mortality was attenuated but still significant (HR 4.05 [3.29-4.97], p<0.001) (Table 4.6).

When controlling for other variables, increasing duration of diabetes (HR 1.01 per 1-year increase [1.01-1.01], p=0.04) and age (HR 1.06 per 1-year increase [1.05-1.07], p<0.001) were associated with a greater risk of mortality at any time over the period. Increasing foot risk showed a very strong association with increasing likelihood of mortality. All categories of foot risk had a positive association with the risk of mortality compared to patients in the low-risk category with the hazard ratio for active/ulcerated group attenuated in the multivariate analysis but still over double at 2.92 [2.25-3.78] (p<0.001). Compared to those within the normal weight category, those in the underweight category were more likely to die although this finding was not statistically significant. Compared to the normal weight category, those within the obese category were significantly less likely to die at any point during the follow up period (HR 0.71 [0.59-0.87] p<0.001).

Table 4.5 Demographic and clinical risk factor variables between survivors and non survivors

Variable (n)		Alive N=1358 (67.1%)	Died n=666 (32.9%)	P value
Amputation		62 (4.6%)	55 (8.3%)	**0.001**
Age		55.2 ±14.2	70.4 ±10.8	**<0.001**
Gender	Men	769 (56.6%)	386 (58.0)	0.60
	Women	589 (43.4%)	280 (42.0)	
Diabetes Type	T1DM	337 (24.8%)	65 (9.8%)	**<0.001**
	T2DM	1021 (75.2%)	601(90.2%)	
Length Diabetes		6.2 (0.1-12.4)	7.3 (1.0-13.6)	**0.04**
WIMD quintile	1	444 (32.7%)	221 (33.2%)	0.18
	2	267 (19.7%)	156 (23.4%)	
	3	259 (19.1%)	114 (17.1%)	
	4	169 (12.4%)	86 (12.9%)	
	5	219 (16.1%)	89 (13.4%)	
Foot risk	Low	860 (63.3%)	240 (36.1%)	**<0.001**
	Increased	358 (26.4%)	275 (41.3%)	
	High	105 (7.7%)	111 (16.6%)	
	Active/ Ulcerated	35 (2.6%)	40 (6.1%)	
Neuropathy	Absent	164 (12.1%)	128 (19.2%)	**<0.001**
	Present	1194 (87.9%)	538 (80.8%)	
PVD	Absent	68 (5.0%)	106 (15.9%)	**<0.001**
	Present	1290 (95.0%)	560 (84.1%)	
Smoking Status	Never	697 (51.3%)	340 (51.1%)	0.58
	Ever	661 (48.7%)	326 (48.9%)	
BMI	Normal Weight	181 (13.3%)	110 (16.5%)	**<0.001**
	Underweight	4 (0.3%)	5 (0.8%)	
	Overweight	369 (27.2%)	212 (31.9%)	
	Obese	796 (58.6%)	337 (50.6%)	
SBP	(mmHg)	140.4 ±17.7	140. ±8 22	0..86
DBP	(mmHg)	80.0 ±8.9	75 ±10.1	**<0.001**
Creatinine	(umol/L)	78 (65.6-90.4)	100 (73.8-126.3)	**<0.001**
Total Cholesterol	(mmol/L)	4.4 ±1.0	4.16 ±1.0	**<0.001**
HbA1c	(%)	8.7 ±1.6	8.6 ±8.4	0.29

WIMD, Welsh Index of Multiple Deprivation; PVD, Peripheral vascular disease; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HbA1c, haemoglobin A1c.

Table 4.6: Unadjusted and full adjusted hazard ratios for mortality (95% CI)

		HR (95% CI) Unadjusted	P value	HR (95% CI) Adjusted	P value
Amputation	No	1.00	**<0.001**	1.00	**<0.001**
	Yes	7.31 (5.37-9.95)		4.05 (3.29-4.97)	
Age		1.07 (1.06-1.08)	**<0.001**	1.06 (1.05-1.07)	**<0.001**
Gender	Women	1.00	0.483		
	Men	1.21 (0.98-1.50)			
Diabetes Type	T1DM	1.00	**<0.001**		
	T2DM	2.29 (1.58-3.31)			
Duration of diabetes		1.00 (1.00-1.00)	0.22	1.01 (1.01-1.01)	**0.04**
Foot risk	Low	1.00		1.00	
	Increased	2.53 (2.03-3.15)	**<0.001**	1.47 (1.24-1.73)	**<0.001**
	High	4.62 (3.42-6.25)	**<0.001**	1.87 (1.52-2.31)	**<0.001**
	Active/Ulcerated	9.09 (5.96-13.85)	**<0.001**	2.92 (2.25-3.78)	**<0.001**
Neuropathy	Absent	1.00	**<0.001**	1.00	0.56
	Present	2.01 (1.53-2.64)		0.95 (0.80-1.13)	
PVD	Absent	1.00	**<0.001**	1.00	**<0.001**
	Present	3.43 (2.57-4.57)		1.55 (1.30-1.85)	
BMI	Normal Weight	1.00		1.00	
	Underweight	2.06 (0.65-6.50)	0.21	1.92 (0.89-4.17)	0.14
	Overweight	1.06 (0.77-1.47)	0.60	0.97 (0.80-1.18)	0.75
	Obese	0.69 (0.51-0.92)	**0.01**	0.71 (0.59-0.87)	**<0.001**
SBP		1.01 (1.00-1.01	0.23		
DBP		0.96 (0.94-0.97)	**<0.001**	0.99 (0.99-1.00)	0.08
Creatinine		1.01 (1.01-1.01)	**<0.001**	1.01 (1.01-1.01)	**<0.001**
Total Cholesterol		0.77 (0.67-0.88)	**<0.001**	0.94 (0.87-1.01)	0.13
HbA1c		0.98 (0.91-1.06)	0.63		

Fully adjusted HRs (age, duration of diabetes, Foot risk, history of neuropathy and PVD, BMI, DBP and total cholesterol). PVD, Peripheral vascular disease; BMI, Body mass index;; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HbA1c, haemoglobin.

4.5 Discussion

This chapter describes a population-based study including all patients diagnosed with diabetes who attended a secondary care diabetes clinic. The main aim of this chapter was to examine the association between social deprivation, BMI and smoking status and amputation secondary to diabetes-related foot disease in a population attending a diabetes secondary care clinic. Although associations were identified for socioeconomic status and BMI these findings were not statistically significant.

In the univariate analysis, when grouped by quintiles, reducing social depravation was associated with a reduced risk of amputation, this was greatest between the most deprived to the least deprived quintile with an OR of 0.55 [0.28-1.05] although this association did not reach statistical significance (p=0.07). When holding the other variables in the analysis constant in the multivariate analysis the association was maintained but again, not statically significant. The trend towards a decreased risk may be related to a number of factors such as self-care, education, occupational risk or nutrition which require further exploration.

The findings within the current literature on the association between social deprivation and amputation risk within the diabetes population are mixed, with some studies reporting a positive correlation (Amin et al., 2014; Shan M. Bergin, Brand, Colman, & Campbell, 2011a; Hippisley-Cox & Coupland, 2015a), some reporting a complicated association (Leese et al., 2013), and some reporting no statistical association (Naseer Ahmad et al., 2014). There is difficulty in comparing the studies due to the variance in populations, socio-economic deprivation calculations and research methodology.

In a similar study to this one, conducted in Tayside performed prospectively looking at a primary care population, a significant association was shown between the Scottish index of multiple deprivation and amputation. However, this was not a straightforward relationship, as the second and fourth most deprived quintiles had the highest risk compared to the least deprived quintile with ORs of 3.37 and 2.51 respectively (Leese et al., 2013). They did however

find a stronger association between foot ulceration and deprivation, with the most deprived quintile having an OR of 1.66 [1.19-2.33] for developing an ulcer compared to the least deprived quintile. This is suggestive of a stronger association between the initial development of foot ulceration and deprivation prior to the progression to amputation. As within this chapter, the number of amputations within the population was small so it may have been that the study was insufficiently powered to see the effect size for amputation. Further investigation is required within a larger population.

The findings of the Tayside study are consistent with whole population studies with universal access to healthcare. In an Australian population, Bergin et al (2011a) investigated the variation in admissions for diabetes-related foot disease including amputation between the most and least deprived social deprivation quintiles. In this population there was a higher rate of admissions for foot ulcer (rate ratio (RR) 1.4 [1.3-1.6]), BKA (RR 1.8 [1.5-2.2]) and AKA (RR 1.35 [0.1-1.9]) in the most deprived quintile, although the relative risk of foot amputation was higher in the least deprived group (RR 0.8 [0.7-1.0]) (Shan M. Bergin et al., 2011a). Statistical significance was not reported within the paper. In the whole prevalent population of people with diabetes in New Zealand those residing in the least-deprived socioeconomic quintile experienced a 34% lower risk of major amputation relative to the most deprived (NZDep quintile 5=reference, NZDep quintile 1, adjusted HR 0.66 [0.49-0.88]) after adjusting for ethnicity, co-morbidity, gender and age(Gurney, Stanley, York, Rosenbaum, & Sarfati, 2018)). The association only held for major amputation with no significant association found between minor amputation and socioeconomic deprivation. This finding was repeated in a Canadian population, with Amin et al (2014) reporting a HR of 1.35 ([1.26-1.44], p <0.001) for amputation in the lowest socioeconomic deprivation group vs the highest in a fully adjusted model including for age, gender, ethnicity and regional variance. However, in a large retrospective cohort study looking at all-cause lower limb amputations in England no association with deprivation was found for amputation with or without a history prior amputation (Naseer Ahmad et al., 2014). There was no specific exploration into variance between risk in patients with and without diabetes and this has yet to be explored within the UK population or within Wales (Naseer Ahmad et al., 2014).

The strength of association between amputation and socioeconomic deprivation may have been affected by the population studied. As discussed in the previous chapter a number of patients that required amputation had not been seen by any secondary care service prior to amputation. Although social deprivation was not explored within the RCA this may have been a factor in why these patients were not referred at an earlier point. In a number of conditions, those from less deprived areas have been shown to have higher rates of referral to secondary care services for treatment, especially in conditions that don't have clear referral pathways(D. McBride, Hardoon, Walters, Gilmour, & Raine, 2010; Mercer & Watt, 2007). A number of factors have been postulated to contribute to the issue such as higher GP workloads in deprived areas and people in deprived areas less likely to advocate for their care. Those from the least socioeconomically deprived areas having a "louder voice" and higher expectations (D. McBride et al., 2010). There is protentional that those from the groups with the highest socioeconomic deprivation may not have been as well represented within the secondary care diabetes clinic.

In the current data, no information on ethnicity was available. One of the limitations of the Tayside study was the absence of ethnicity as a variable. Having an ethnicity other than white British has been shown to be inversely correlated with amputation risk in UK populations (Chaturvedi et al., 2002; Holman et al., 2012), but positively correlated with deprivation (StatsWales, 2019). It is possible that the effect size seen in this chapter may have been greater if the effect of ethnicity had been controlled for. However, as discussed previously, Wales is less ethnically diverse than the areas covered in previous studies looking at social deprivation with only 6.3% of residents who are not White British or Irish within the whole Wales population and 8.1% of residents who are not White British or Irish within Swansea (Public Health Wales Observatory, 2015).

The associations of foot risk, peripheral vascular disease, SBP, creatinine and HbA1c with amputation confirm previous findings (Edward J. Boyko et al., 2018; Kim, Shin, Roh, Chang, & Lee, 2017; Leese et al., 2013). In a meta-analysis of predictive laboratory findings, increasing HbA1c, WBC, CRP and erythrocyte sedimentation rate (ESR) and decreasing haemoglobin (Hb)

were associated with amputation risk in a diabetes population (Kim et al., 2017). HbA1c was dichotomised into high (>8%) and low risk groups (<8%) with a OR for amputation of 5.65 [3.39-9.45], p <0.001 for the high-risk group. In keeping with the results of our analysis, cholesterol was not found to be significant in determining the risk for amputation. Although not significant in our study there was an inverse association between increasing cholesterol and amputation. This trend was also seen when looking at foot risk in a previous paper on this secondary care population with those in the high foot risk category having significantly lower cholesterol compared in the low foot risk category (4.1mmol/L:4.3mmol/L, high risk:low risk, p=0.03) (R. Thomas et al., 2010b). This may be due to malnutrition associated with disease severity (Zhang et al., 2013). This was reflected in the inverse association between BMI and amputation. When stratified into categories being underweight was associated with a trend towards increased risk of amputation (OR 2.50 [0.07-84.95], p=0.07). Although neither finding was statistically significant, this may have been due to sample size and warrants further investigation.

The lack of association with smoking status was an interesting finding as there is substantial evidence indicating smoking is a risk factor for cardiovascular disease (Daar et al., 2007), hypertension (A. Virdis, Giannarelli, Neves, & Ghiadoni, 2010) and is a major risk factor for PVD in the diabetes and non-diabetes population (Thiruvoipati et al., 2015). PVD is one of main pathways to diabetes-related amputation (NICE, 2016) and was shown to be associated with amputation risk in this secondary care population and in the previous chapters analysis of major amputation. A recent meta-analysis by Lu et al found the association between smoking and PVD was greater than that for smoking and coronary heart disease (Lu, Mackay, & Pell, 2014). An association between smoking and foot ulceration has also been reported, another major pathway to amputation (NICE, 2016). In a recent meta-analysis Liu et al found smoking was associated with diabetes foot amputation (M. Liu, Zhang, Yan, & Yuan, 2018) with an OR of 1.65 [1.09-2.50], p<0.01; however the study did not investigate any differences between populations or look at any potential confounding variables in their analysis.

Theoretically there are a number of reasons why smoking would increase the risk of amputation, with detrimental effects on would healing, its association with PVD in patients with and without diabetes, it's known association with CHD and stoke in people with diabetes and its proven association with neuropathy (Solomon Tesfaye et al., 2005). Despite this the evidence for its effect on amputation risk in patients with diabetes is contradictory and scarce. Most studies that do explore smoking as a risk of amputation in patients with diabetes are small cohort studies and do not control for other variables. A recent meta-analysis reported that smoking increased the risk of amputation, however this publication contained mainly small cohort studies and could not control for other variables (M. Liu et al., 2018). The findings of this chapter did contradict the findings of the meta-analysis, and it may be that the sample size was too small, as the odds were headed towards an increase risk. This requires investigation with a larger study but as discussed earlier smoking is coded poorly in routine health data.

Thomas et al (2010b) did not find a significant association between smoking status and foot risk when investigating the same population used in this chapter. A smaller proportion of patients were active smokers in high foot risk group compared to those in the lowest risk group (17.7% vs 14% p=0.33). It may be that the smoking intervention policies are targeted at active or high foot risk patients, but this occurs too late in the disease process for the reversal of risk produced through quitting to have an effect on outcome. For CVD the risk of a cardiovascular event occurring among ex-smokers decreases towards that of never smokers with increasing time from cessation, with no significant difference in risk seen at 10 years (Huxley et al., 2012). The effect of the length of cessation of smoking on amputation risk has never been examined in the population with diabetes. As smoking status is more likely to be underreported with greater stigmatisation of smoking (Liber & Warner, 2017), it is also possible that patients may be less likely to report smoking if they already have complications as they will be more exposed to smoking cessation literature and advice.

The mortality rate of those undergoing amputation was high with 47% of the patients who underwent amputation dying by the end of the study period. 20.5% of patients died within 1-

year of the amputation and 42.7% within 5 years. The mortality rate was lower than seen in other population studies of similar design with a 1 year mortality rate of 36% reported by Gurney et al (2018) and 44% by Fortington et al (2013). This may be due to the variation in follow-up time after amputation in this study. Follow-up was only one year for 10 patients (8.6%), two years for 15 patients (12.8%) and three years for 13 patients (11.1%). It may be that these patients would go on to die in the subsequent years. There was a significant association between amputation and death despite the high rate of death in the population that did not receive amputation, with 32% mortality in this group over the study period. The high mortality rate in the non-amputation group is likely due to characteristics of the secondary care patient population. It may be that some of these patients would have required amputation if they had a better prognosis.

4.6 Limitations

The main limitation to this study is the small sample size of 117 amputations. It was not possible to assess for mediation between factors due to this as this can lead to overfitting of models due to sample size. If models are over-fitted this results in bias as there is an upper limit of complexity a model can accept before spurious and unrepeatable findings are generated (Babyak, 2004). The data were observational and not prospectively collected as part of a trial, and thus may be prone to selection bias. In addition, some patients did not have foot risk scores recorded at the time of the study, and we have used a multiple imputation approach in dealing with the missing data. The study was undertaken on a secondary care specific sample so findings may not be generalisable to the general population with diabetes. In addition, all amputations types were examined together as It was not possible to stratify amputation by type for the analysis in this chapter due to the small number of amputations. If powered, distinguishing major from minor amputations may have been revealing. There was varying follow up for mortality after amputation and a small sample size so it was not possible to investigate further associations with mortality. Cause of death and the effect of ethnicity on amputation risk and its interaction with socioeconomic deprivation were not explored in the study. It is, however, a population-based study and reflects routine clinical practice.

CHAPTER FIVE

Knowledge, behaviour and expectations of foot care of persons with diabetes in the Swansea locality

5.1 Introduction

The majority of research relating to risk factors for amputation in diabetes-related foot disease has been directed towards identifying medical factors that put patients at a high risk. It is widely accepted that a number of pathological risk factors such as previous ulceration, neuropathy, foot deformities and lesions, and suboptimal diabetes control increase the risk for foot ulceration and amputation (NICE, 2016). This has led to the annual foot review with foot risk calculation becoming standard practice, as demonstrated by inclusion in the Primary Care Quality and Outlook Framework system (NHSDigital, 2017).

However, this is not the complete picture and there is less high-quality information within the available literature to identify if there are high-risk behavioural, socioeconomic or educational factors, which influence amputation rates. Despite patient education becoming a cornerstone of non-medical intervention, the literature on its effectiveness was identified as inconclusive by NICE due to the low volume and poor quality of studies (NICE, 2016). The findings from the RCA performed in chapter three identified that patient factors contributed to every amputation that occurred. A proportion of this was due the complexity of disease at presentation, however failure to attend appointments, poor medication or treatment compliance, late presentation with foot disease and refusal of intervention contributed in 62.5% of cases. Although the mechanisms that lead to these outcomes are complex and varied (Brewster, Bartholomew, Holt, & Price, 2020; Delea et al., 2015; Khan, Lasker, & Chowdhury, 2011) they have been shown to be modifiable with knowledge of disease (Adams, 2010).

NICE and Diabetes UK both view foot care education as an integral role in management of diabetic foot disease. Diabetes UK in its recent 'Putting feet first' position statement highlighted the importance of patients with diabetes being involved in their own care with an emphasis on patient knowledge of foot care behaviours, risk of complications and awareness of what their health service should provide (Diabetes UK, 2015c). Despite this, large population-based studies have highlighted that a quarter of diabetes patients may never examine their feet (Johnston et al., 2006; Safford et al., 2005). This rate has been shown to

vary between populations, globally, and between age groups (Chen et al., 2018). This is thought to be due to cultural and education factors and may in part be due to a lack of knowledge.

Knowledge is defined as a confident understanding of a subject, with the potential to use it in a specific context (Sørensen et al., 2012). It has been observed in cross-sectional studies around the world that knowledge explains some of the variance in foot care behaviour (Dorresteijn, Kriegsman, Assendelft, & Valk, 2014; Ede, Eyichukwu, C. Iyidobi, & C. Nwachukwu, 2018; Johnston et al., 2006) and can account for some variance in practice along with educational level and gender. Although the role of education in preventing ulcers and amputation is not conclusive, a recent systematic review of the evidence concluded that education may have positive, if short-lived, effects on foot care knowledge and behaviour (Dorresteijn et al., 2014). Further high quality randomised controlled trials are needed. This is a view reflected by NICE, concluding that the evidence surrounding the role of educational measures for those at risk of diabetic foot problems was limited, inconclusive and further investigation is required (NICE, 2016). As the prevalence of diabetes increases worldwide, if education can be used to improve knowledge and influence protective behaviours this could offer an affordable preventative strategy in the development of foot ulcers and ultimately amputation.

Full conclusions cannot be drawn from the current evidence on the benefit of education due to the use of unvalidated tools for measuring knowledge and behaviour and short follow-up periods that allow only for identification of short-term changes in knowledge or behaviour, not changes in medical outcomes such as ulceration (NICE, 2016). In order to address this, studies using validated tools such as the Nottingham Assessment of functional footcare (NAFF) (Lincoln, Jeffcoate, Ince, Smith, & Radford, 2007) to assess knowledge and behaviour are required as well as longer follow up periods.

At present there is a sparsity of literature evaluating patients foot care knowledge and behaviour across the spectrum of diabetic foot disease and within the Welsh population. Previous studies looking at knowledge and behaviour have shown considerable variances between populations even within the western world (Chen et al., 2018). Variances are found within age groups, education level and culture. It has been documented that at present there is little consistency in the foot care education provided to people with diabetes, with those considered low risk often receiving little or none, especially on information relating to complications and their prevention (McInnes et al., 2011). It cannot be assumed that evidence of knowledge and behaviour from disease-free patients is generalisable to patients with ulcers (Vedhara et al., 2014). There are also reported variances in the ability to perform foot care, driven by lack of support systems, access to care i.e. rural populations, disability and health and understanding of education (Bell et al., 2005).

There is variance in the literature between countries indicating that the evidence is not generalisable. With no previous data from the Welsh population and variance in structures of care between each health board, identifying the baseline level of education received by patients is important before any changes in practice can be implemented. This is especially true within the Swansea locality as large gaps in the knowledge base were identified within the RCA as demonstrated by delays in presentation and treatment. The effect of knowledge on foot care behaviours has not been evaluated and investigating patients foot care knowledge and behaviour from health to amputation could help identify areas in which further education programmes would have greatest impact within the health board.

5.2 Aims and objectives

Although guidance on diabetes foot care is an expectation every time a patient engages with the diabetes service (NICE, 2016), adherence to these guidelines has never been investigated within ABMU. From the RCA described in the previous chapter it was identified that a proportion of patients who underwent amputation were not known to diabetes services prior to their amputation or had not attended foot review appointments on several occasions. A lack of knowledge regarding the importance of diabetes foot care may be a contributing factor to this late presentation or non-attendance.

In order to establish ways to improve the service and the education provided to patients we must first evaluate the knowledge our patients currently have, and the behaviours undertaken, as they move through the health care system.

The study specific aims of the chapter are:-

(i) To explore the relationship between knowledge and behaviour in different risk, socioeconomic groups and genders within the population.

(ii) To identify foot care and general diabetes knowledge and behaviour in our population and clinical and psychosocial factors which may influence this.

(iii) To explore patients' perceptions of the current service and patients' expectations and ideas on what education the service should provide.

5.3 Methods

5.3.1 Sample

The study was a cross sectional survey conducted in primary and secondary care clinics from October 2018 to January 2019. All patients attending a single primary care centre and all secondary care clinics within the ABMU health board were eligible for sampling. A convenient random recruitment method was utilised (Lavrakas, 2008). As the population of people with diabetes within ABMU is 33000 a minimum sample size of 380 was calculated using the Cochran formula (Shodhganga, 2013). People aged 18 years or over, with T1DM or T2DM who had been diagnosed with diabetes at least 6 months prior, attending either a secondary care clinic or primary care facility for routine diabetes review were eligible for inclusion (Table 5.1). The aim was to recruit equal numbers of patients from each setting and a random sample of each stage of foot disease - healthy, diabetes-related foot disease and amputated, representative of patients attending the clinics. The primary care clinic consisted of a practice nurse and a podiatrist and the secondary care clinics consisted of a diabetes consultant or registrar and podiatrist with access to DSN and a dietician. All patients in secondary care were revived by a podiatrist at least annually and primary care patients with any foot care risk above low risk (NICE, 2016) were reviewed by a podiatrist at least annually.

5.3.2 Experimental design

The study was conducted using a self-administered questionnaire. This could be completed in a paper or online format. Primary and secondary care clinics were attended by the researcher, and patients were approached in the waiting room to participate in the study during their regular diabetes review whilst waiting for clinical review. The questionnaire explained the background and intention of the study and consent was assumed if the questionnaire was completed (appendix IV). The majority of the patients approached in the clinics accepted the invitation. Patients who did not speak English, were new to the area, had a diagnosis for less than 6 months, had bilateral amputation, those who declined to participate and those unable to complete the questionnaire due to comprehension were not included in the study (Table 5.1).

Best effort was made to make the questionnaire in a large print but if the patient could not read the questionnaire or write their answers, due to loss of sight, or physical disability, the questionnaire was delivered verbally, face to face, and answers were written verbatim. No extra visual cues to question answers were given by the researcher and participants were given sufficient time to answer questions without probing for answers so as not to influence the participant.

Table 5.1 Inclusion and exclusion criteria for questionnaire study

Inclusion Criteria	Exclusion Criteria
Patients with diabetes attending 1° or 2° care clinic	Unable to comprehend questionnaire due to:
>18 years of age	Visual impairment
Diagnosis of diabetes >6months in duration	Cognitive impairment
English Speaking	Language Barrier.
Attending ABMU for at least one annual review	Bilateral Amputation.
	Diagnosis of diabetes <6months
	New patient to ABMU.

1°: Primary; 2°: Secondary; ABMU: Abertawe Bro Morgannwg University Health Board

A total of 398 participants were included. The study was approved as a service-based evaluation by the health board Department of Research and Development and Swansea University Joint Clinical Research Committee (appendix I).

5.3.2.1 Questionnaire

The questionnaire was comprised of three sections and could be completed within 5 to 15 minutes (appendix IV):-

(i) Part one of the questionnaire contained questions on gender, age, education level, current diabetes care and foot care diagnosis, perception of whether the participant had received

foot care education, who this was from and knowledge of the participants current foot care risk. Patients were recorded as having diabetes-related foot disease if they self-reported a history of neuropathy, PVD, Charcot foot, ulcer or amputation.

(ii) Part two consisted of three previously tested structured questionnaires.

Patients foot care knowledge was assessed using a pre-tested, structured questionnaire prepared from the recommendation of the American College of Foot and Ankle Surgeons and Diabetes UK as used and validated in previous studies of a similar design including a similar UK based population (Pollock, Unwin, & Connolly, 2004). Each question was scored 1 for a correct response and 0 for an incorrect response with a maximum score of 11.

General diabetes knowledge was assessed using the Michigan Revised Diabetes Knowledge test (DKT) (Collins, Mughal, Barnett, Fitzgerald, & Lloyd, 2011) which consists of 23 items suitable for people who use insulin and an initial 14 items suitable for all people with a diagnosis of diabetes. As the demographic information within the questionnaire did not identify medication use, the study used only the 14-item questionnaire. Each question was scored 1 for a correct response and 0 for an incorrect response with a maximum score of 14. The questionnaire was validated for use in both south Asian and white Caucasian populations within the UK to assess a patient or populations overall knowledge of diabetes, making it appropriate for the population of Swansea with 94% of residents white and 0.8% of the population being Bangladeshi, the largest non-white ethnic population within the region (ONS, 2012). It was expected that the proportion of the south Asian population attending diabetes clinic would be higher than the proportion within the general population as T2DM is 6 times more common in people of south Asian descent (Diabetes UK, 2010). The questionnaire contains 2 questions pertaining to diabetes foot care knowledge, regarding caring for feet and knowledge of neuropathy and it was expected that the scores on these questions would correlate with the foot care knowledge score questionnaire.

Foot protective behaviour was assessed using the Nottingham Assessment of functional footcare (NAFF), a questionnaire intended to assess the level of people's preventive self-care

behaviours (Senussi, Lincoln, Jeffcoate, & Thomas, 2011). It was designed to identify people who were not engaging in recommended foot care practice and used in studies of a similar design as a tool to assess footcare behaviour (Lincoln et al., 2007). The tool showed good test-retest, psychometric and internal reliability and has been used on a variety of populations with diabetes including those with different levels of foot disease. The tool consists of 26 questions with 4 answers per question. Each question scores between 0 to 3 for least to most appropriate answer, with a maximum score of 78. In the validation study, a score under 50 indicated poor foot care behaviours (Senussi et al., 2011).

(iii) The third part of the questionnaire explored peoples' perceptions of the current service and their expectations and ideas on what the service should provide through three short answer and three free text questions to allow for more in-depth responses.

The questionnaire was reviewed by a clinical psychologist and diabetes consultant for internal validity before circulation and was piloted on 10 patients. After this pilot the questionnaire was re-formatted to include a questionnaire for foot risk and correct minor grammatical errors in the foot knowledge questionnaire.

5.3.3 Statistical analysis

For comparison of baseline variables and questionnaire scores, the chi-squared test was used for categorical variables. Pearson's correlation and Spearman's rank correlation were used for normally and non-normally distributed continuous variables respectively. A calculation of odds ratios for univariate analysis and multiple logistic regression was performed to find variables significantly associated with knowledge and behaviour questionnaire scores. Categorical variables were tested as potential predictors of scores: gender, education level, age, history of foot problem, history of amputation, foot care education, primary or secondary care provision and continuous variables were tested for correlation.

Multivariate analysis was then performed using linear regression with a forward stepwise selection process; factors were included if they had <0.2 significance in their univariate analysis to account for negative confounding. Multivariate analysis was used to assess the effect of knowledge score on behaviour when controlling for other factors that correlated with knowledge scores, DKT scores and NAFF scores individually (Cohen & Cohen, 1983). No statistical approach, such as multiple imputation was used to address missing data as it was unclear from the data if question answers were missing at random. To address missing data when it is not missing at random can introduce bias into an analysis as it can modify or amplify associations which have not been controlled for within the analysis (BMJ, 2009).

5.4 Results

5.4.1 Participant characteristics

A total of 398 participants accepted the invitation to complete the questionnaire in clinic; despite best efforts to encourage completion of the questionnaire some people declined, and some questionnaires were returned partially completed. There was a response rate of 98.2% (n=391) for part one of the questionnaire, 98.5% (n=392) for the foot care knowledge questions, 78.6% (n=313) for the DKT and 93.7% (n=373) for the NAFF. Responses for the knowledge and behaviour questions were only included if the section was completed in full. The number of responses in each analysis is noted throughout.

The mean age of patients with fully completed responses was 58.8 years (range: 19-88 years) (Table 5.2). People in the partially completed questionnaire group had a significantly higher mean age (65.5 years (range: 24-90 years), $p<0.001$). Fifty five percent (n=160) of full respondents were men, 60.6% (n=163) of the full responders' group had received secondary education and 36.4% (n=98) had further education. Of the full responders, 33.3% (n=97) reported a history of foot problems with 63 of those reporting diabetes-related foot disease (21.6%) and 15 reporting an amputation (5.1%). The people who partially responded reported a statistically significantly higher rate of previous foot problems and diabetes-related foot disease (21.6% vs 39.8% (n=39), $p<0.01$) and there was a statistically significant difference in education level between the two groups ($p<0.01$). There was no statistically significant difference in any other baseline variables.

Table 5.2. Demographic data for participants with fully and partially completed questionnaires.

	Fully completed n=293	Partially completed n=105	P value
Age (years)*	58.83 (57-60.7)	65.5 (62.76-68.2)	**<0.001**
Men (%)	160 (54.6%)	54 (56.3%)	0.78
Education level (%)			**<0.001**
Primary School	8 (3%)	9 (11.1%)	
Secondary School	163 (60.6%)	58 (71.6%)	
Higher Education	98 (36.4%)	14 (17.3%)	
Diabetes related foot disease (%)	63 (21.6%)	39 (39.8%)	**<0.001**
Self-reported foot problem (%)	97 (33.3%)	48 (49%)	**0.006**
Amputation (%)	15 (5.1%)	2 (2%)	0.20
Minor	11	0	
Major	4	2	
Care provider (%)			0.12
GP	77 (26.3%)	216 (73.7%)	
Secondary Care Clinic	36 (34.3%)	69 (65.7%)	
Received foot care education (%)	183 (63.5%)	60 (65.2%)	0.77
Know foot risk (%)	128 (44.1%)	36 (37.9%)	0.29

Data are presented as count (%) * Data are presented as median and IQR.

The proportion of participants with foot problems in primary and secondary care was evenly split with 24.8% (n=28) of primary care population and 26.0% (n=74) of secondary care population reporting diabetes-related foot problems (Table 5.3). There were no statistically significant differences between the number of men in primary care versus secondary care (54.0% vs 53.7%), education level, history of amputation and knowledge of current foot risk. Participants from primary care were significantly older (69 years (range: 60.4-77.6) vs 61 years (range: 49.5-72.5 years), p<0.001) and were significantly less likely to report having received foot care education (38.9% vs 42.1%, p=0.01). There was an equal distribution of men and women with diabetes related foot disease (25.7% of women and 26.4% of men) in the whole population.

Table 5.3. Demographic data for participants recruited from primary and secondary care cohorts

	Primary care n=113	Secondary care n=285	P value
Age (years)*	69 (60.4-77.6)	61 (49.5-72.5)	**<0.001**
Men (%)	61 (54.0%)	153 (53.7%)	0.81
Education level (%)			0.05
Primary School	7(6%)	10 (3.5%)	
Secondary School	67(59.3%)	154 (54.0%)	
Higher Education	22 (19.5%)	90 (31.6%)	
Diabetes related foot disease (%)	28 (24.8%)	74 (26.0%)	1.00
Self-reported foot problem (%)	42 (37.2%)	103 (36.1%)	0.77
Amputation (%)	2 (1.8%)	15 (5.3%)	0.23
Minor	1	10	
Major	1	5	
Received foot care education (%)	56 (49.6%)	187 (65.6%)	**0.01**
Know foot risk (%)	44 (38.9%)	120 (42.1%)	0.73

Data are presented as count (%) * Data are presented as median and IQR.

In the whole population the most frequently self-reported foot problem was neuropathy (12.6%, n=49) (Table 5.4) followed by ulceration (11.8%, n=46).

Table 5.4 Self-reported foot care problems

	n=389(%)		n(%)
Foot ulcer	46 (11.8)	Flat foot	2 (0.5)
Charcot foot	8 (2.1)	Plantar fasciitis	10 (2.6)
PVD	32 (8.2)	Arthritis	2 (0.5)
Ischaemic limb	3 (0.8)	Fungal infection	5 (1.3)
Neuropathy	49 (12.6)	Other	26 (6.7)
Ingrowing toenail	9 (2.3)		

Data presented as count (%)

5.4.2 Knowledge of foot care

A total of 392 (98.5%) participants completed the foot care knowledge section of the questionnaire (Table 5.5). The maximum score was 11 with a minimum of 0. The median score was 9 (range: 7-11). As there were only five responses missing, the sample was too small for statistical differences between the responders and non-responders. The lowest scoring question was number 11-frequency of shoe checking, with only 43% (n=169) of respondents answering correctly. The second lowest scoring question was question 6-frequency of foot checking, with only 62.5% (n=245) of patients aware of frequency required to check feet.

Table 5.5 Response to knowledge questions

n=392	Correct (%)	Incorrect (%)
DM patients should take medication regularly because they are liable to get DM complication.	358 (91.3)	34 (8.7)
DM patients should look after their feet because they may not feel a minor injury to their feet.	370 (94.4)	22 (5.6)
DM patients should look after their feet because wounds and infection may not heal quickly.	377 (96.2)	15 (3.8)
DM patients should look after their feet because they may get a foot ulcer.	339 (86.5)	53 (13.5)
DM patients should not smoke because smoking causes poor circulation and affects the feet	359 (91.6)	33 (8.4)
How often do you think you should inspect your feet?	245 (62.5)	147 (37.5)
If you found redness/bleeding between your toes what is the first thing you do?	317 (80.9)	75 (19.1)
Even if you have never had a corn/ hard skin lesion, what would you do if you had one	280 (71.4)	112 (28.6)
How often do you think your feet should be washed?	349 (89)	43 (11)
What temperature of water do you think you should wash your feet in?	302 (77)	90 (23)
How often do you think you should inspect the inside of your footwear for objects or torn lining?	169 (43.1)	223 (56.9)

Data presented as count (%); DM: Diabetes Mellitus

5.4.2.1 Association of demographic factors with foot knowledge score

In univariate analysis female gender, attending a secondary care clinic, having received foot care education and a participant being aware of their current foot risk were significantly associated with knowledge score (Table 5.6) Women had a significantly higher median knowledge score of 10 (9-11) compared to men with 9 (8-10), p=0.02. Participants that attended secondary care has a significantly higher median knowledge score than those attending primary care (9 (8-10) vs 9 (7.5-10.5), p<0.001). Those who had previously received foot care advice had a significantly higher knowledge score that those who had not (9 (8-10) vs 9 (7.5-10.5), p<0.01). Those who received foot care education scored better in every question but with the same variation in results and participants who knew their foot risk had a significantly higher knowledge score than those who did not (median 9 (8-10) vs 9 (8-10) p=0.007). There was no statistically significant difference in median score for people with any self-reported foot disease, diabetes related foot disease or amputation.

Table 5.6 Analysis of association between Foot care knowledge and demographic data

Variable		number	Knowledge score (IQR)	P value
Age (years)		385		0.73*
Gender	Men	385	10 (9-11)	**0.02[x]**
	Women		9 (8-10)	
Education Level	Primary	347	8.5 (7.9-9.1)	0.51[x]
	Secondary		9 (8-10)	
	Higher		9 (8-10)9 (8-10)	
Foot problem general	No	385	9 (8-10)	0.92[x]
	Yes		9 (8-10)	
Diabetes foot disease	No	385	9 (8-10)	0.11[x]
	Yes		9 (8-10)	
Amputation	No	387	9 (8-10)	0.66[x]
	Yes		9 (8-10)	
Care provider	Primary	392	9 (7.5-10.5)	**<0.001[x]**
	Secondary		9 (8-10)	
Received foot education	No	376	9 (7.5-10.5)	**<0.001[x]**
	Yes		9 (8-10)	
Aware of foot risk	No	381	9 (8-10)	**0.007[x]**
	Yes		9 (8-10)	

*Spearman rank. [X]Mann-Whitney U

5.4.2.2 Multivariate Analysis

When controlling for other variables, knowledge score was significantly associated with gender, care provider and receipt of foot care education. The multiple regression model predicted 12.4% of knowledge score (F (6,331) =7.89 R^2=12.4%, p<0.001). Three of the variables added statistically significantly to the prediction, gender, care provider and receipt of foot education. Regression coefficients with CI can be found in Table 5.7.

Table 5.7. Summary of linear regression analysis for Foot care knowledge score. univariate and multivariate.

Variable	Univariate regression		Multivariate regression	
	B	P value	B	P value
Intercept			7.89	<0.001
Age	0.01 [-0.01-0.02]	0.25		
Gender	-0.35[-0.68--0.01]	**0.04**	-0.38 [-0.72--0.05]	**0.03**
Education Level				
Primary	ref		ref	
Secondary	0.23 [-0.61-1.07]	0.59	0.16 [-0.64-0.96]	0.69
Higher	0.38 [-0.48-1.25]	0.38	0.25 [-0.59-1.08]	0.56
Foot Problem	0.11 [-0.23-0.46]	0.52		
Diabetes foot disease	0.39 [0.01-0.76]	**0.05**	0.30 [-0.08-0.68]	0.12
Amputation	-0.04 [-0.85-0.76]	0.91		
Care Provider	0.71 [0.35-1.08]	**<0.001**	0.60 [0.22-0.98]	**0.002**
Received foot education	0.97 [0.64-1.31]	**<0.001**	0.82 [0.47-1.18]	**<0.001**
Aware of foot risk	0.52 [0.19-0.86]	**0.002**	0.31 [-0.05-0.67]	0.10

B= unstandardized coefficient, [CI] = 95% CI

5.4.3 Knowledge of general diabetes – Michigan Revised Diabetes Knowledge test

A total of 313 (78.6%) participants completed the DKT section of the questionnaire (Table 5.8). The maximum score was 14 with a minimum of 2. The mean score was 9.86 ±2.23 (70% ±20%). There was no variance in the demographic characteristics between those who fully completed the questionnaire and those who did not (appendix IV). The lowest scoring question was number 4 'Which of the following is a "free food"?'-with 32.9% (n=103) of respondents answering correctly. The was followed by question 8 'Which should not be used to treat a low blood glucose?'-with 41.5% (n=130) of respondents answering correctly

Table 5.8 Response to Michigan DKT questions

Question (correct answer) n=313	Correct (%)	Incorrect (%)
The diabetes diet is: (b. a healthy diet for most people)	259 (82.7)	54 (17.3)
Which of the following is highest in carbohydrate? (c. Baked potato)	199 (63.6)	114 (36.4)
Which of the following is highest in fat? (a. Low fat (2%) milk)	160 (51.1)	153 (48.9)
Which of the following is a "free food"? (d. Any food that has less than 20 calories per serving)	103 (32.9)	210 (67.1)
HbA1c is a measure of your average blood glucose level for the past: (c.6-12 weeks)	150 (47.9)	163 (52.1)
Which is the best method for home glucose testing? (b. Blood testing)	263 (84)	50 (16)
What effect does unsweetened fruit juice have on blood glucose? (b. Raises it)	192 (61.3)	121 (38.7)
Which should not be used to treat a low blood glucose? (c.1 cup diet soft drink)	130 (41.5)	183 (58.5)
For a person in good control, what effect does exercise have on blood glucose? (a. Lowers it)	263 (84)	50 (16)
What effect will an infection most likely have on blood glucose? (b. Raises it)	254 (81.2)	59 (18.8)
The best way to take care of your feet is to: (a. look at and wash them each day)	304 (97.1)	9 (2.9)
Eating foods lower in fat decreases your risk for: (c. heart disease)	285 (91.1)	28 (8.9)
Numbness and tingling may be symptoms of: (b. Nerve disease)	248 (79.2)	65 (20.8)
Which of the following is usually not associated with diabetes: (d. lung problems)	279 (89.1)	34 (10.9)

Data presented as count (%); HbA1c: haemoglobin A1c

5.4.3.1 Association of demographic factors with the Michigan Revised Diabetes Knowledge test

The DKT score was not normally distributed so nonparametric tests were used. Reducing age, increasing education level and attending a secondary care provider significantly increased the chance of having a higher DKT score (Table 5.9).

In the univariate analysis (Table 5.10), age explained 10.4% of the variance in knowledge scores ($p<0.01$). Age statistically significantly predicted knowledge score, $F(1, 304) = 35.356$, $p<0.01$; as age increased, DKT score decreased. The median knowledge scores for the participants where their highest level of education was Primary school, Secondary school and Higher education were, 7.5 (6.5-7.5), 10 (8.5-11.5) and 11 (9-13) respectively and there was a significant difference in distributions of scores between the groups ($p<0.001$). It was not possible to assess difference in medians as the variance between the groups was different. Patients that attended secondary care had a significantly higher DKT score than those attending primary care (10 (8.5-11.5) vs 9 (7.5-10.5), $p<0.001$).

There was no significant difference in scores between genders, those with and without self-reported general or diabetes related foot disease or in those with or without amputation. Participants who had previously received advice didn't have significantly higher knowledge score that those who had not (10 IQR [8.5-11.5] vs 10 IQR [8-12], $p=0.42$). Those participants who had not received education scored higher in question 2, 3, 4, 8 and 9. The two questions pertaining to foot care -

Q11 - how to take care of feet; those who had received education answered correctly more frequently, 98.9% vs 93.69%, and this was statistically significant $p=0.02$.

Q13 - numbness and tingling is a symptom of nerve disease; was again answered correctly more by those who had received education 81.1% vs 77.5%, although this was not significantly significant, $p=0.49$.

There was a significant correlation between the foot care knowledge score and the DKT score (p=0.047) although foot care knowledge score only explained 2.2% of the variance in DKT score (coefficient 0.112 (0.029-0.195 p<0.01).

Table 5.9 Analysis of association between DKT score and demographic data

Variable		number	DKT (IQR)	P value
Age (years)		306		**<0.001***
Gender	Women	307	10 (8.5-11.5)	0.64[x]
	Men		10 (8.5-11.5)	
Education Level	Primary	280	7.5 (6.5-8.5)	**<0.001[x]**
	Secondary		10 (8.5-11.5)	
	Higher		11 (9-13)	
Foot problem general	No	305	10 (8-12)	0.15[x]
	Yes		10 (8.5-11.5)	
Diabetes foot disease	No	305	10 (8-12)	0.37[x]
	Yes		10 (8.5-11.5)	
Amputation	No	307	10 (9.5-11.5)	0.43[x]
	Yes		10 (8-12)	
Care provider	Primary	313	9 (7.5-10.5)	**<0.001[x]**
	Secondary		10 (8.5-11.5)	
Received foot education	No	301	10 (8-12)	0.42[x]
	Yes		10 (8.5-11.5)	
Aware of foot risk	No	303	10 (8.5-11.5)	0.07[x]
	Yes		10 (8.5-11.5)	

*Spearman rank. [X]Mann-Whitney U

5.4.3.2 Multivariate analysis

When controlling for other variables using multivariate liner regression DKT score was significantly associated with age, education level and care provider. The multiple regression

model predicted knowledge score (F(6,267)=14.5. R^2=24.6%, p<0.001) in 24.6% of cases. Foot care knowledge score was not included in the analysis as the scores were highly correlated and measure some of the same outcome. Three of the variables added statistically significantly to the prediction; age, education level, and diabetes care provider. Regression coefficients with CI can be found in Table 5.10.

Table 5.10. Summary of linear regression analysis for DKT score, univariate and multivariate.

Variable	Univariate regression		Multivariate regression	
	B	P value	B	P value
Intercept			9.76	<0.001
Age	-0.05 [-0.06-0.03]	**<0.001**	-0.04 [-0.05--0.02]	**<0.001**
Gender	-0.08 [-0.59--0.43]	0.75		
Education Level				
Primary	ref		ref	
Secondary	1.99 [0.52-3.47]	**0.01**	1.64 [0.15-3.13]	**0.03**
Higher	3.38 [4.44-4.88]	**<0.001**	2.59 [1.06-4.12]	**<0.001**
Foot Problem	-0.48 [-1.78-0.08]	0.08	-0.22 [-0.72-0.29]	0.40
Diab foot disease	-0.30 [-0.91-0.31]	0.33		
Amputation	-0.55 [-1.73-0.62]	0.35		
Care Provider	1.08 [0.53-1.63]	**<0.001**	0.86 [0.30-1.41]	**0.003**
Received foot education	0.32 [-0.22-0.8]	0.24		
Aware of foot risk	0.56 [0.05-1.07]	**0.03**	0.18 [-0.29-0.66]	0.45

B= unstandardized coefficient CI = 95% CI

5.4.4 Behaviour - Nottingham Assessment of Functional Footcare

A total of 372 (93.7%) participants completed the behaviour section of the questionnaire. Table 5.11 shows the response to the individual behaviour questions. The maximum score was 68 with a minimum of 25. Each question was scored from 0-3 for the least to the most appropriate option; therefore, for the 372 participants the maximum score for each question was 1116 if all respondents answered correctly. The mean score was 50.44 ±6.93 (64.7% ±8.9%). There was no statistically significant difference in demographic data between those who did not complete the questionnaire and those who did (appendix IV).

The lowest reported performed behaviour was question 1 'how often do you examine your feet' with respondents scoring 40% of total marks, although 174 participants (46.8%) did report that they check their feet every day. Question 3 'do you check shoes when take-off' also performed badly with 61.3% of participants checking shoes never or rarely. Only 43.8% of participants reported never putting on moisturising cream on their feet. A number of high-risk practices were reported by the study population including putting moisturising cream in between their toes; 41.9 %. Fifty-two percent of participants reported that they never put a dressing or plaster on a blister and only 33.3% reporting using a dressing on a graze, cut or burn. A large proportion of participants reported wearing slippers with no fastenings (55.9%).

Table 5.11 Response to Behaviour questions

Behaviour n=372	0 (%)	1 (%)	2 (%)	3 (%)	Score (%)
Examines feet	108 (29.0)	85 (22.9)	174 (46.8)	5 (1.3)	448 (40)
Check shoes when putting on	49 (13.2)	49 (13.2)	103 (27.7)	171 (46.0)	768 (69)
Check shoes when taking off	109 (29.7)	119 (32.0)	93 (25.0)	50 (13.4)	455 (41)
Wash feet	41 (11.0)	71 (19.1)	237 (63.7)	23 (6.2)	614 (55)
Dry feet	8 (2.2)	15 (4.0)	75 (20.2)	274 (73.7)	987 (88)
Dry between toes	23 (6.2)	47 (12.6)	54 (14.5)	248 (66.7)	899 (81)
Put moisturising cream on feet	163 (43.8)	41 (11.0)	81 (21.8)	87 (23.4)	464 (42)
Avoid moisturising cream between toes	69 (18.5)	54 (14.5)	33 (8.9)	216 (58.1)	768 (69)
Regularly cut toenails	10 (2.7)	82 (22.0)	215 (57.8)	65 (17.5)	707 (63)
Wear slippers with fastenings	209 (56.2)	44 (11.8)	25 (6.7)	94 (25.3)	376 (34)
Wear trainers	114 (30.6)	48 (12.9)	109 (29.3)	101 (22.2)	569 (51)
Wear shoes with fastenings	57 (15.3)	29 (7.8)	86 (53.5)	200 (53.8)	802 (72)
Avoid wearing pointed toed shoes	11 (2.9)	42 (11.3)	62 (17.7)	257 (69.1)	937 (84)
Avoid wearing flip flops or mules	37 (9.9)	109 (29.3)	60 (16.1)	166 (44.6)	727 (65)
Break in shoes gradually	78 (21.0)	89 (23.9)	106 (28.5)	99 (26.6)	598 (54)
Avoid artificial fibre socks	67 (18.0)	109 (29.3)	79 (21.2)	117 (31.5)	618 (55)
Avoid wearing shoes without socks/tights	45 (12.1)	80 (21.5)	54 (14.5)	193 (51.9)	767 (60)
Change socks daily	26 (7.0)	35 (9.4)	300 (80.6)	11 (3.0)	668 (60)
Avoid walking inside barefoot	63 (16.9)	102 (27.4)	61 (16.4)	146 (39.3)	662 (59)
Avoid walking outside barefoot	2 (0.5)	38 (10.2)	42 (11.3)	289 (77.7)	989 (89)
Avoid using a hot water bottle	12 (3.2)	25 (6.7)	33 (8.9)	302 (81.2)	997 (90)
Avoid putting feet near fire	5 (1.3)	12 (3.2)	32 (8.6)	323 (86.8)	1045 (94)
Avoid putting feet on radiator	1 (0.3)	15 (4.0)	24 (6.5)	332 (89.2)	1059 (95)
Avoid using corn remedies/plasters	11 (3.0)	19 (5.1)	30 (8.1)	312 (83.8)	1015 (91)
Use a dry dressing on a blister	196 (52.7)	53 (14.2)	77 (20.7)	46 (12.4)	345 (31)
Use a dry dressing on a graze, cut or burn	125 (33.6)	76 (20.4)	111 (29.8)	60 (16.1)	478 (43)

Data presented as count (%); Question percentage out of 372; Score percentage out of total 1112

5.4.4.1 Association of demographic factors with the NAFF

The behaviour score was not normally distributed so nonparametric tests were used. Male gender, a self-reported foot problem, a diabetes foot problem, attending a secondary care clinic, having received foot care education, foot knowledge score and DKT score significantly increased the chance of performing protective foot care behaviour (Table 5.12)

Men had a significantly higher median knowledge score of 52 (48.5-55.5) compared to women with 51 (46.5-55.5) (p=0.004). Participants with any self-reported foot disease had a significantly higher median score of 53 (49-57) compared those without foot disease with 51 (47-55) (p=0.003). This was also true for those participants with diabetes foot disease (53(48.5-57.5) vs 51(47-55), p=0.004). Participants that attended secondary care had a significantly higher NAFF score than those attending primary care (52 (47.5-56.5) vs 50 (45.5-54.5), p=0.002) and those who had previously received advice had a significantly higher score that those who had not (52 (47.5-56.5) vs 50 (45.5-54.5), p<0.01).

Footcare knowledge score was significantly correlated with behaviour (p<0.001) and foot care knowledge score explained 14.2% of the variance of behaviour scores (p<0.001) (Figure 5.1).

The DKT score and behaviour were also found to be correlated (p=0.02) although the DKT score only explained 1.1% of the variance in behaviour score (p=0.07) (Figure 5.2).

Table 5.12 Analysis of association between NAFF score and demographic data

Variable		number	NAFF (IQR)	P value
Age (years)		363		0.77*
Gender	Women	363	51 (46.5-55.5)	**0.004**[x]
	Men		52 (48.5-55.5)	
Education Level	Primary	329	51 (44.5-57.5)	0.55[x]
	Secondary		51 (47-55)	
	Higher		52 (48-56)	
Foot problem general	No	363	51 (47-55)	**0.003**[x]
	Yes		53 (49-57)	
Diabetes foot disease	No	363	51(47-55)	**0.004**[x]
	Yes		53 (48.5-57.5)	
Amputation	No	365	51 (46.5-55.5)	0.21[x]
	Yes		53 (46.5-59.5)	
Care provider	Primary	372	50 (45.5-54.5)	**0.002**[x]
	Secondary		52 (47.5-56.5)	
Received foot education	No	335	50 (45.5-54.5)	**<0.001**[x]
	Yes		52 (47.5-56.5)	
Aware of foot risk	No	360	51 (47.0-55.0)	0.22[x]
	Yes		52 (47.5-56.5)	
Foot care Knowledge				**<0.001***
DKT				**0.02***

*Spearman rank. [X]Mann-Whitney U

Figure 5.1 Correlation between Foot care knowledge and NAFF score

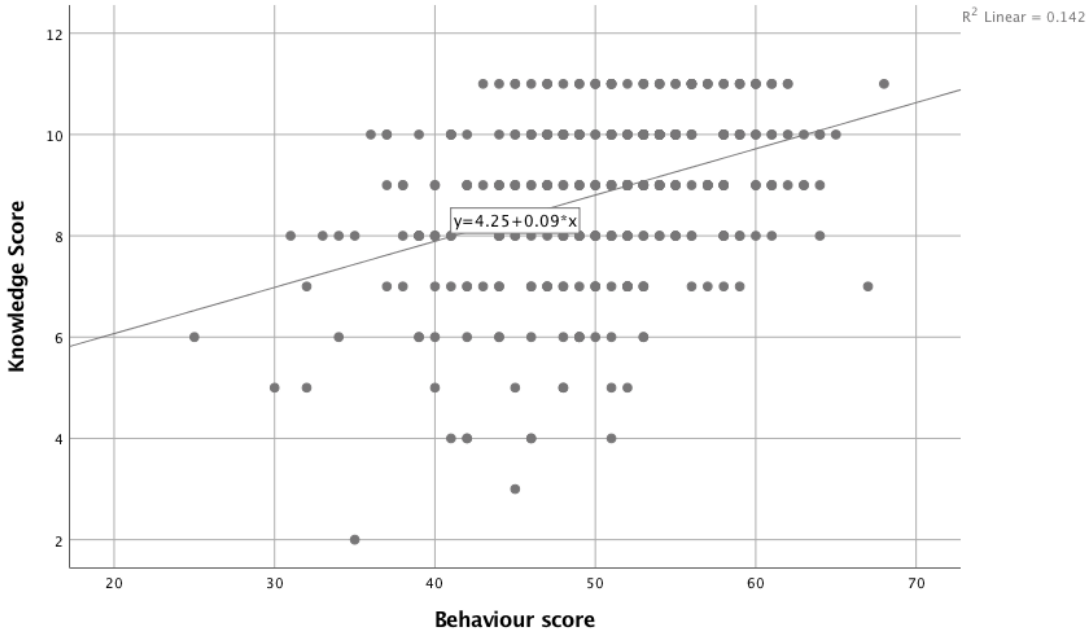
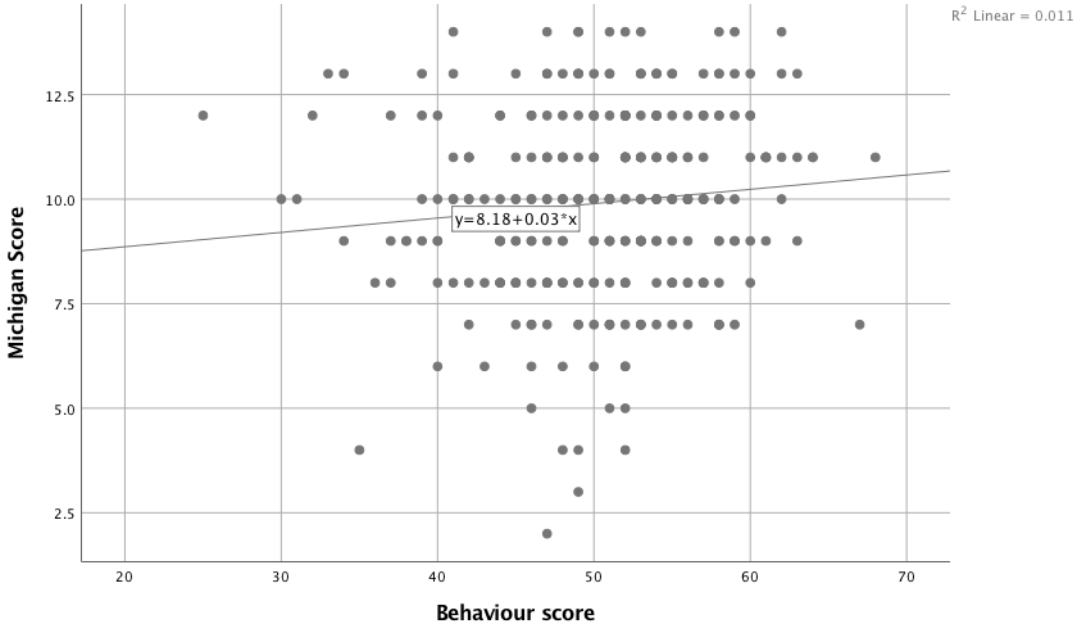


Figure 5.2 Correlation between DKT and NAFF score



5.4.4.2 Multivariate analysis

A multiple regression analysis was run to predict NAFF score from gender, history of diabetes-related foot problem, care provider, previously receiving foot care information and either DKT score or foot care knowledge score as the scores were highly correlated. Regression coefficients with CI can be found in Table 5.13

The multiple regression model with foot knowledge score included, predicted behaviour score ($F(5\text{-}344)=18.121$. $R^2=20.8\%$, $p<0.001$). The regression model with DKT score also predicted behaviour but to a lesser extent ($F(6\text{-}279)$ $R^2=8.4\%$, $p<0.001$). Foot knowledge score remained significantly associated with behaviour score after controlling for other predictors of behaviour ($p<0.001$). Other variables significantly associated with a higher behaviour score were male gender and diabetes care provider.

The variance in NAFF score associated with a history of receiving foot education may be explained by knowledge score and a history of diabetes foot problem. As shown above, participants who had previously received foot care education had significantly higher knowledge scores. Those participants who had a diabetes foot problem were also more likely to receive footcare education ($p=0.012$). Despite this, the effect of foot care knowledge on behaviour was still significant when adjusting for receiving education.

Table 5.13. Summary of linear regression analysis for NAFF score, univariate and multivariate

Variable	Univariate regression		Multivariate regression Foot Knowledge Score		Multivariate regression DKT	
	B	P value	B	P value	B	P value
Intercept			33.64	<0.001	43.74	<0.001
Age	0.01 (-0.03-0.06)	0.59				
Gender	2.16 (0.74-3.58)	**0.003**	2.91 (1.57-4.25)	**<0.001**	1.99 (0.43-3.48)	**0.01**
Education Level						
Primary	ref					
Secondary	1.64 (-1.83-5.11)	0.35				
Higher	1.89 (-1.69-5.48)	0.30				
Foot Problem	2.33 (0.87-3.80)	**0.002**			-	
Diab foot disease	2.39 (0.77-4.01)	**0.004**	1.38 (-0.19-2.96)	0.09	1.73 (-0.18-3.64)	0.08
Amputation	3.02 (-0.35-6.39)	0.08	1.32 (-1.88-4.51)	0.42	1.67 (-1.89-5.23)	0.36
Care Provider	2.49 (0.95-4.02)	**0.002**	1.50 (-0.003-3.00)	**0.05**	1.18 (-0.60-2.96)	0.19
Received foot education	3.00 (1.51-4.49)	**<0.001**	1.20 (-0.24-2.64)	0.10	2.80 (1.20-4.39)	**<0.001**
Aware of foot risk	0.79 (-0.67-2.24)	0.29				
Foot Knowledge Score	1.56 (1.17-1.95)	**<0.001**	1.48 (1.05-1.90)	**<0.001**		
DKT	0.32 (-0.03-0.67)	0.07			0.25 (-0.09-0.60)	0.15

5.4.5 Advice

Receipt of footcare education was self-reported by 243 participants (61.1%). Table 5.14 presents the breakdown of the health care practitioners reported to have provided education. Of those participants with previous diabetes-related foot disease, 74.5% (n=77) had received foot care education, significantly more than those without foot disease (60.5% (n=179), p=0.012).

Of those participants with a history of amputation, 70.6% (n=12) had received foot care education. This was not significantly greater than participants without a history of amputation (p0.56). Participants who had received foot care education reported greater foot care behaviours with significant variance in NAFF score, as well as a statistically significantly higher knowledge score.

Table 5.14 Practitioner group delivering foot care education

Practitioner type	n=243 (%)
Practice nurse	61 (25.1)
GP	29 (11.9)
Podiatrist	161 (66.3)
Diabetes specialist nurse	99 (40.7)
Consultant or member of hospital team	36 (14.8)

The barriers to preventing participants performing foot care practices reported in free text responses included poor eyesight, arthritis and lack of awareness of need to assess feet. This was documented in the patient views segment of the questionnaire.

Participants completed section 3 of the questionnaire on views of the service in 85.6% of cases (n=333). Education was reported to be adequate by 255 participants (76.6%). Twenty five percent of the 333 participants who responded wanted to see a change in the education provided by the health board. This was despite only 61.1% (n=185) of participants reporting that they had ever received foot care education in the first section of the questionnaire. Participants expressed a wish to see a varied range of education strategies (Table 5.15) with the largest proportion of participants (30.4%) indicating that they would prefer face-to-face education.

Table 5.15 Type of foot care education participants would like to see

Education type	n=217 (%)
All/Any	17 (7.8)
Text	28 (12.9)
Online	45 (20.7)
Teaching session/face to face	66 (30.4)
Pamphlets	47 (21.7)
Phone for advice	2 (0.9)
Film/TV	3 (1.4)
Other	9 (4.1)

5.5 Discussion

This study was a cross sectional survey of persons attending for diabetes annual review in primary and secondary care clinics. The central aim of this chapter was to examine the association between knowledge and behaviour within the population. Foot care knowledge was significantly positively correlated with behavioural score even after controlling for gender, history of diabetes foot problems and diabetes care provider. This association was in keeping with the findings of other similar studies in a number of other countries (Indrayana, Guo, Lin, & Fang, 2019; Rajan, Pogach, Tseng, Reiber, & Johnston, 2007; Shrestha, Aacharya, Shrestha, & KC, 2017). It is, however, difficult to compare studies as different questionnaires were used to asses knowledge and, when similar questionnaires were used, arbitrary definitions of good and bad knowledge/ practice were utilised to complete analysis (Seid & Tsige, 2015). No previous studies have been performed comparing knowledge and practice in a similar population to this one, however, the studies within different populations used multivariate analysis and therefore should be comparable in part as some differences in population have been controlled for. In keeping with the results of this chapter, studies in all populations found a positive association between improving foot care knowledge and self-reported behaviour at least in the short-term.

The second outcome of the study was to assess the difference in knowledge and behaviour score at different levels of foot disease. History of diabetes-related foot disease was significantly associated with higher knowledge and behaviour score, but no significant relationship was found with amputation. There was a positive association between history of amputation and higher knowledge and behaviour scores, but it did not reach statistical significance. In a larger American study of 728 patients, amputation was strongly positively associated with foot care behaviour after controlling for age, race, knowledge and history of neuropathy (Olson et al., 2009). The lack of significance in this chapter may then have been due to the small number of participants who had undergone amputation within the population studied.

The foot care knowledge score only predicted 21% of the variance in the NAFF score indicating other factors play a role in a determining a person's health related behaviours. Previous research has shown associations between self-efficacy, personal health, and support systems and health behaviours (Bell et al., 2005). Self-efficacy is a patient's confidence in their ability to perform health behaviours. Sarkar et al (Sarkar, Fisher, & Schillinger, 2006), found that a person's self-efficacy will influence which foot care behaviours they engage in. The authors reported that, after controlling for other factors, higher self-efficacy scores improved the odds of performing foot protective behaviours by 22%. This finding was replicated by McCleary-Jones et al (McCleary-Jones, 2011), who demonstrated a significant association between self-efficacy and foot care behaviour. However the literature is mixed with studies demonstrating no significant association between self-efficacy and self-care (Wendling & Beadle, 2015).

Health beliefs may also affect behaviour; Vedhara et al(2014), in a small prospective qualitative study, found patient belief to account for between 42% and 58% of variance in foot care behaviours, even after controlling for ulcer size and symptoms. In another small prospective study, participants with diabetes-related foot disease who did not receive support with caring for their feet but had adequate self-efficacy, had better foot practices overall (McCleary-Jones, 2011). Dependence on formal or informal support reduced the ability of the participants to perform foot care independently._This may relate to self-determination theory whereby persons are thought to be more competent when autonomously motivated, through enhanced perceived competence (Patrick & Williams, 2012).

In this study many participants reported a need for more support in cutting nails. Although this is likely due to an elderly population, it is worth considering that this may reduce autonomy. In a study of older adults, receiving support reduced foot care index scores (Bell et al., 2005). Although this study used a different scoring system for foot care activities, the finding supports the view that proper patient education can improve foot self-care even in an

elderly population with mobility issues and encouraging persons to be self-sufficient increases the likelihood that these behaviours will be performed.

Difficulties in performing tasks in this study were similar to those reported in other developed countries. Harwell et all found that 9% of participants did not check their feet daily due to poor vision or physical limitation (Harwell et al., 2001). Pollock et al found that physical barriers to performing recommended foot care practice were joint mobility problems (13%), difficulty in toenail trimming (9%) and visual impairment (2%). Although self-care may improve self-efficacy, there is a risk as those persons with diabetic foot disease are more likely to have physical limitations. The presence of diabetic foot disease is associated with increasing age and other co-morbidities and limitations associated with these, such as reduced mobility or poor eyesight, may prevent self-care behaviours. Many persons attended clinic with their family members, and a few noted in the free text section of the questionnaire that they wished foot care knowledge to be disseminated to family members and carers to help assist with protective behaviours.

This work has provided data on 97.7% of respondents to classify their history of diabetes-related foot disease allowing for a snapshot of the current population attending diabetes annual review clinics. Of these, almost 26.2% reported previous or current diabetes foot disease. The lifetime neuropathy risk within the sampled population of 12.6% was less than that reported in the literature of 50% (Juster-Switlyk & Smith, 2016). The lifetime prevalence of foot ulcers of 11.8% was higher than the risk in the UK population as reported by NICE (10%) (NICE, 2016) but within previous population based estimates from similar surveys, which reported a range between 9-28%. (Pollock et al.; Walters, Catling, Mullee, & Hill, 1992). The prevalence of amputation at 4.3% was higher than previously reported in similar surveys in the UK at 2.1% (0.5-3.6%)(Pollock et al., 2004) and 1.3% (0.6-2.0%) (Walters et al., 1992). This is in keeping with the known higher rate of amputation within the area although this was a random sample and only representative of persons attending one primary care and a sample of secondary care clinics, so cannot be taken as representative of the whole Swansea population.

The tertiary aim of the study was to assess the current level of knowledge on general and foot specific diabetes care and the foot protective behaviours performed within the population. The mean basic knowledge score of the respondents of 8.83 (±1.68) was higher than reported in previous studies within the UK using the same questionnaire (6.5 ±2.1) (Pollock et al., 2004). However, less that 43% of participants were aware of the necessity to check shoes before wearing, or the need to check feet regularly. Although higher than that found within a study in an English population (Pollock et al., 2004), the finding is still of concern as these are simple measures that can reduce the risk of amputation. The second lowest scoring knowledge question was related to the appropriate frequency of foot checking, with only 63% of participants aware of the required frequency. The outcome of the questions corresponded with the reported behaviour from the NAFF questionnaire. Only 184 of 378 (49%) of participants reported checking their feet once a day or more, again indicating a relationship between knowledge and behaviour and highlighting a neglected simple protective behaviour.

In keeping with other studies in the UK, a higher knowledge score was significantly associated with receiving foot care education and having a history of foot problem. It has been demonstrated previously that those persons with low-risk feet are unlikely to receive any information relating to foot complications and how to avoid them (McInnes et al., 2011). Litzelman et al found that when persons were known to have high risk feet, providers were more likely to offer preventative services as a whole (Litzelman et al., 1993). Although evidence is inconclusive as to whether education reduces the risk of ulceration, education has been shown to improve foot care knowledge and protective self-reported self-care behaviour in the short term(Dorresteijn et al., 2014) and is a cornerstone of current guidelines. Excluding low-risk persons potentially excludes a group from an easily implemented risk reduction strategy. However, it is possible that those persons with a higher knowledge score may have had a greater capacity to remember the advice they had received. Therefore, it is possible that the results may represent misreporting from those persons who had forgotten they had received advice.

No association between knowledge or behaviour scores and educational attainment was demonstrated within the chapter. Studies that have demonstrated an association between formal education attainment and foot care knowledge score were in developing countries, where populations had much greater levels of persons reporting education only up to primary school level. It may be that difference in populations explains the variance or that access to basic foot care knowledge is more widely available in developed countries.

For the Michigan DKT score, the average score within our population was 70% (±16%). This was lower than reported in the original validation study for the questionnaire (77% ±20%). Concerning findings from this study were that 52.1% of participants were unaware of what a HbA1c tests meant and 58.5% were not able to identify the correct product to treat a hypoglycaemic episode. The Michigan DKT score was significantly associated with formal education attainment, suggesting that the latter affects the ability to retain general diabetes knowledge more than foot care knowledge. The foot care knowledge questionnaire was significantly associated with the receipt of foot care education although the DKT questionnaire was not. This is suggestive of specific education for foot care will increase footcare knowledge, and foot care can be taught regardless of formal education attainment as shown by the lack of association between education level, foot care knowledge score and behaviour.

The Michigan DKT score was not associated with foot care behaviours when controlling for other factors. In a meta-analysis of seven studies looking at health literacy, no association was found between general health literacy and foot self-care (Chen et al., 2018). Despite this, it is possible that general diabetes knowledge is associated with amputation through a route other than behaviour, as poor glycaemic control is associated with amputation(E J Boyko et al., 1999) and low Michigan DKT scores are associated with poor glycaemic control(Al-Qazaz et al., 2011; Panja, Starr, & Colleran, 2005). At present there is an absence of studies that investigate the association between amputation and general diabetes knowledge when controlling for foot care knowledge and potentially behaviour. It is unclear whether foot risk

is modifiable if general diabetes knowledge is poor regardless of adequate foot care knowledge. This may explain in part the finding that men performed significantly more foot care protective behaviours, but we know from epidemiological studies, that men have a significantly greater risk of diabetes foot disease and amputation (PHE, 2019). No significant association was found between general diabetes knowledge and behaviour on multivariate analysis and this may indicate the need for specific rather than general education. However, it is possible that the lack of association was due to the poor response for the DKT with a response rate below the sample size calculation.

Less than half the participants reported knowing their own foot risk (41.2%). This was far below the expected NICE standards as knowledge of foot risk is one the key outcomes of an annual foot review (NICE, 2016) therefore every patient should have been aware. It is not possible to determine from the questionnaire whether foot risk was not being assessed during the review, if participants were not being informed of their foot risk or whether the information was not being retained. If participants were not being informed or the assessment was not being performed this would put participants at risk of not receiving education, as risk stratification has been shown to influence protective care given (Litzelman at al., 1993), and if people cannot advocate for their own care they are less likely to be engaged with preventative care (Hilliard et al., 2015). This finding was reflected in the fact that participants in this study who had previous foot ulceration were more likely to report they had received foot care education as their risk was clear to practitioner and patient.

Many of the free text comments noted that there was a lack of education in different languages. Although this study did not explore ethnicity, this is in keeping with the findings of qualitative studies that have demonstrated foot care knowledge in ethnic minority groups in the UK to be poor (Collins et al., 2011). There is a clear need for education to be available in different languages with support groups to reach this population.

5.6 Summary and limitations

Diabetes foot disease is responsible for considerable morbidity and mortality within the Health Board. Progression to ulceration and amputation is preventable. This study highlights areas of foot knowledge, general diabetes knowledge and practice that are deficient within the population. It has identified practices that put persons at risk of developing foot problems and the barriers within the service to the performance of protective behaviours. Over 20% of participants were dissatisfied with the education provided, highlighting an area for improvement. If performed in the way that persons are most likely to respond to, this should effect behaviour and ultimately diabetes-related foot disease prevalence and outcomes over time.

5.6.1 Clinical significance

Knowledge questionnaires can be used as a measurement tool for the quality of foot care education that is being provided by the service as knowledge has been shown to improve behaviour in this and previous studies (Dorresteijn et al., 2014; Rajan et al., 2007; Wendling & Beadle, 2015) . By having understanding of baseline knowledge and behaviour, this could help in directing services to those most in need of education or those most at risk of poor outcomes. By routinely measuring the scores the questionnaire could act as a measure of knowledge and practices over time. If the correct answers were provided after the questionnaire was given it could also act a regular reminder of good practice without the need for expensive teaching sessions.

5.6.2 Limitations

One of the major limitations was uncompleted questionnaires: although missing responses are typical in survey research it resulted in a sample size for the DKT questionnaire lower than the adequate sample size calculated. There is potential for selection bias as those non-respondent participants may be those with the lowest levels of confidence and knowledge. Best efforts were made to ensure questionnaires were completed by the individual alone but as most participants attended with a carer or family member and questionnaires were completed within the waiting room there is a possibility that participants may have received

help from others. When questionnaires were completed by the interviewer there was potential for bias from non-verbal cues.

Outcomes of the study were self-reported and so participants may have over- or under-reported disease status, access to education services and responses to behavioural practices through deficiencies in recall or providing answers that they felt were socially acceptable. This may have been a greater factor in questionnaires completed by an interviewer than those completed individually. As it wasn't documented which questionnaires were completed face-to-face it is not possible to assess for this in the analysis. Other studies have shown diabetes diagnosis and procedures are reliably reported in populations with similar demographics and the rate of neuropathy was similar to studies using formal assessment of neuropathy and medical notes. It is also possible that the amputation may have been for reasons other than diabetes-related foot disease as this was not assessed for in the demographic data.

Other risk factors that were found to be significantly associated with knowledge and behaviour of diabetes foot care in some studies such as length of diabetes, insulin use, socioeconomic status and occupation were not assessed in this study. That may lead to confounding that is unable to be controlled for. As the study population was predominately from a clinic it is possible that the level of knowledge and practices do not reflect the whole population the health board serves.

CHAPTER SIX

Utilising the SAIL database to examine the incidence of lower limb amputation in people with and without diabetes in Wales between 2008-2018

6.1 Introduction

As discussed in chapter 1, literature reporting the incidence of amputation within Wales is sparse. Establishing time trends from the available data from within the UK is difficult due to methodological differences in definitions of age groups, populations, and amputation variance in the use of standardisation as well as differing methods in the presentation of results. There is marked variability in the incidence rates between health boards within England (Naseer Ahmad et al., 2014; PHE, 2019) and regions of Scotland (Kennon et al., 2012) and between the countries of the UK. it is not possible to assume that rates within England will be comparable to rates within Wales.

Ahmed et al (2014) noted a large variance between the incidence rate of amputation between Northern (31.7 amputations/ 100 000 person years (PY)) and Southern (23.1 amputations /100 000 PY) England, which persisted over time despite the falling rates of amputation in England in general. This trend was identified in populations with and without diabetes. Similar variance has been noted in other developed countries, with up to an 8.6-fold variation in the incidence of major amputation between states within the USA (J. S Wrobel et al., 2001) and a 2-fold variation seen between university hospital districts in Finland (K. Winell, Venermo, Ikonen, & Sund, 2013a).

At present, the data received from NWIS relating to amputation incidence and prevalence in the diabetes population in Wales are not age- or sex-standardised and only provide data for all amputations. It is not possible to assess if there is true variance in amputation rate between health boards or if changes seen in the population with diabetes are as a result of a changes in the size of the population in each area (Boulton et al., 2005; NWIS, 2017). The variation seen within the NWIS data may reflect differences in health care delivery or may be due to inherent differences in demographics between the populations. To examine this variance the incidence rate in Wales as a whole must be established and then rates within the health boards must be explored controlling for changes in size and demographic makeup of each population. It has been demonstrated that those regions with higher amputation rates for people with diabetes also have higher amputation rates in general. Assessing amputation rates for people with and without diabetes will allow us to explore if differences reflect differences in service provision for the two populations.

6.2 Aims and Objectives

At present there is no study that examines the incidence rate of lower extremity amputation within the Welsh population. Although a number of strategies to improve amputation rates in the diabetes population have been introduced regionally (Kanade et al., 2007) and nationally (Diabetes UK, 2015c) changes in amputation rates over time have not been explored.

6.2.1 Aims

The specific aims of the chapter are to:-

(i) Examine trends in incident and total lower extremity amputation rates among people aged 17 years and over with and without diabetes, between 2008-2018 using nationwide data.

(ii) To describe diabetes and non-diabetes related lower extremity amputation incidence rates and to determine the influence of diabetes on the relative risk of amputation (major, minor, any) in the Welsh population.

(iii) To examine for regional variation in age- and sex-standardised amputation (major, minor, any) rates, time trends and diabetes risk between health boards.

6.2.2 Objectives

The specific objectives of the chapter are:-

Objective 1. Examine the Influence of diabetes on lower limb amputation rates

1.1 To calculate incidence and total rates across the population with and without diabetes for:-

a) Major lower limb amputation

b) Minor lower limb amputation

1.2 To identify a link, if any, between rates of minor and major amputation by diabetes presence unadjusted and adjusted for demographic risk factors.

Outcome Measures:

1. The incidence rate, per 10 000 PY of major lower limb and minor lower limb amputation in the population with and without diabetes

2. To calculate the odds of having an amputation with diabetes compared with those without diabetes unadjusted and adjusted for demographic risk factors.

3. To calculate major minor amputation ratio in each population

Objective 2. Examine the Influence of geographical location on lower limb amputation

2.1 To calculate incidence rate by health board in the populations with and without diabetes;

a) Major lower limb amputation

b) Minor lower limb amputation

2.2 To identify a link, if any, between rates of major and minor amputation across Wales

2.3 To determine whether regional differences in amputation can be accounted for by differences in the demographic profile of populations

Outcome Measures:

1. The prevalence rate, per 10 000 PY of major and minor lower limb amputation in each health board

2. To calculate the odds of having an amputation with diabetes in each health board unadjusted and adjusted for demographic risk factors

3. The major minor amputation rate in each health board

6.3 Methods

6.3.1 Study population and data assessment

Data were extracted from SAIL, a secure anonymised information linkage databank, maintained by the health informatics research unit at Swansea University. SAIL is a repository of routine medical data primarily focused on the residents of, or people receiving services, in Wales from primary, secondary and outpatient settings.

Patients are represented within the database by an anonymised linking field (ALF), based on their NHS number, name, sex, date of birth and postcode. This allows researchers to track a person's interaction with any service, intervention or dataset and accurately link these within the databank (Lyons et al., 2009). It allows for construction of population level patient cohorts. People in the databank without an ALF were excluded from the study.

This study primarily used clinical data from the Welsh Longitudinal General Practice database (WLGP), the Patient Episode Database for Wales (PEDW) and the Outpatient Database for Wales (OPDW). Nonclinical data were extracted from the Office of National Statistics (ONS) annual district birth extract (ADBE) and annual district death extract (ADDE) as well as the Welsh Demographic Service Database (WDSD). Any events, admissions or services received prior to December 2018 were included. All amputations between 2008-2018 were taken into account regardless of cause in line with other national publications and PHE analysis (Naseer Ahmad et al., 2016; Claessen et al., 2018; PHE, 2019).

People with diabetes were identified using an established algorithm (J. Rafferty et al., 2018; J Rafferty et al., 2021) utilising linked data from several clinical and non-clinical sources within SAIL. People were classified as having diabetes if a diabetes code was present across any of the databases. To assess for the accuracy of the algorithm in T1DM, it was validated using data from a local diabetes register for children with diabetes in Wales. Those in the study population were included in the WDSD at entry into the study and either remained in Wales for the study period or were censored as they died or moved out of Wales. People were

considered to have diabetes from first registration of diabetes, patients with gestational diabetes were excluded.

PEDW was used to identify amputations performed in all people with diabetes over 17 years of age. Persons aged 17 years and over were included as per PHE analysis (PHE, 2019). Relevant classification of Office of Population, Census and Surveys interventions and procedures version 4 (OPCS4) codes were identified within the database. PEDW summarises all standard hospital admissions and day-case activity undertaken in NHS Wales, plus data on Welsh residents treated in English NHS Trusts (NHS Wales, 2020). It includes demographic data, diagnosis (primary, related and associated using International Classification of Diseases 10 (ICD10) codes) and procedures (coded using OPCS4 codes). The database does not include private admissions; however, it is unlikely an amputation would occur within a private hospital setting as the procedure often occurs during an emergency admission. Amputations were defined as major if above the ankle (OPCS4 codes: X09:X095, X098, X099) and minor if through or below the ankle (X10:X11.9) (National Vascular Registry, 2018). Procedures on amputation stumps (X12), which included re-amputations at a higher level were not included in the incidence rates but were used within the observation period to identify a history of amputation. Persons without a documented week of birth (WOB) were not included. Laterality, the side on which the procedure was performed, was not assigned as there was no data available on the accuracy or frequency of laterality codes used within PEDW. Amputations were identified as incident if no record of amputation was found within a 5-year lookback period (Rosenlund et al., 2020). Amputation type was determined within the lookback period and a person was included in the incident major amputation analysis if they had previously undergone a minor amputation but not if the opposite was true due to the aetiology of the amputation types.

A person's health board at entry into the study was derived from their registered home address at time of admission using 2011 LSOA unitary authorities. LSOAs are built from groups of Output Areas derived from postcodes used for the 2001 Census and updated in 2011. There are 1,896 LSOAs in Wales, each with a population of about 1,500 people. If the LSOA had changed between 2001-2011 and the patient only had a documented 2001 LSOA the closest approximate 2011 LSOA was used. Health board was assigned based on the Unitary Authority

boundaries to Local Health Board 2014 descriptor from the ONS. No accommodation was made for changes to health board boundaries that came into effect in 2019.

Access to the SAIL databank was granted by the SAIL Collaboration Review System. The collaboration review system consists of the SAIL Management Team and an Information Governance Review Panel (appendix I). Ethical approval or written consent from individuals was not required as only anonymised data was used and no linking to primary data was intended.

6.3.2 Statistical Analysis

All analysis was undertaken using R (R version 3.6.1 2019) and figures were produced using the package ggplot2 (Wickham, 2016).

Analyses were performed for the entire population, population with diabetes and population without diabetes, stratified by gender, for any lower limb amputation and for major and minor amputations individually. The annual amputation rate per 10 000 PY was estimated with number of incident or total amputation per individual as the numerator. The denominator was derived from ONS Wales mid-year population estimates (ONS, 2019). The denominator for the diabetes population was the cumulative person years at risk for all people identified as having diabetes in the respective year. The age specific non-diabetes population was then obtained by removing the age specific diabetes population from the ONS entire population estimate.

Incident any, major and minor amputation rate was computed counting only first major or minor amputations occurring per person within the period. If an incident major and incident minor amputation occurred in 1 person with diabetes within 1 year the first amputation be it minor or major was counted in the any analysis and the patient was counted in both incident minor and incident major analysis. An amputation was determined to be attributable to diabetes if the person was identified as having diabetes prior to or within 3 months of amputation, as per a previous publication (Kennon et al., 2012). Total any, major and minor amputation rates were calculated by counting all amputations a person received within a year regardless of whether this was an incident or recurrent amputation.

Annual direct age-sex-standardised rates for the whole population were calculated, and age standardised amputation rates for sex-specific evaluation were calculated using age categories 17-24, 25-44, 45-64, 65-74, 75-84 and 85+ years. The ONS Wales mid-year population estimate for 2013 was used as the population for standardisation.

The incident amputation number and crude and standardised incident amputation rate with confidence intervals [ ] in the total population (ARt), among people in the population with diabetes (ARd) and in subjects in the population without diabetes (ARn) were calculated for 'incident any', 'incident major' and 'incident minor' amputations. Amputation rate ratios were calculated for diabetes and non-diabetes populations using the direct standardised rates (DSR). Confidence intervals for the DSRs were calculated using Dobson & Byar's method (PHE, 2010). Comparisons in amputation rate were made between the 2008-2010 period and the 2016-2018 periods by calculating a DSR ratio and confidence interval using the DSR package within R (Kumar, 2019). Standard errors for directly standardised rates were calculated in the package using Chiang's (1961) method. The total number of amputations and crude and standardised total amputation rates for 'all any', 'all major' and 'all minor' amputations per year were also calculated within the populations described.

The relative risk of an individual with diabetes undergoing amputation (minor, major, and any) compared with that of an individual without diabetes was calculated with confidence intervals calculated using the delta method (PHE, 2010). Major-Minor amputation ratio was calculated for rolling 3-year periods of incident amputation rates to reduce variation caused by yearly fluctuations, as these were unlikely to reflect significant changes in clinical care.

In order to compare the changes in the trends of amputation over the time period, the indicator values in each year were compared to the baseline incidence in 2008. Each indicator had a value of one for the year 2008 and changes were measured in relation to the baseline year. Poisson regression was used to look at the effect of year on amputation and all models were assessed for over dispersion.

For the first and last 6-year time period of the study direct age-sex-standardised amputation rates for incident all, major and minor amputation for the total, diabetes and non-diabetes populations within each health board were calculated using age categories 17-64,65-79, 80+ years. Numbers were too small to divide the age categories further. To examine variance between health boards and over time, rates for the entire time period were calculated and the rate ratio comparing the two time periods was used to assess if there was a significant change between the periods. The ONS Wales mid-year population estimate for 2013 was used as the standard population. Amputation rate ratios were calculated between diabetes and non-diabetes populations using the direct standardised rates (DSR). Confidence intervals for the DSRs were calculated using the Dobson & Byar's method (PHE, 2010).

6.4 Results

The results are divided into 3 main sections: 6.4.1-6.4.3. Section 6.4.1 describes the whole study population and the crude number of major, minor and total amputation. Section 6.4.2 describes the incidence rate of any, major and minor incident and total lower limb amputation in the population with and without diabetes and the influence of diabetes on risk of amputation (objective 1). It also describes major-minor amputation ratio for the whole of Wales. Section 6.4.3 describes the incidence of major lower limb amputation across health boards and the influence of diabetes on risk of amputation (objective 2). It also describes major-minor amputation ratio within the different health-boards.

6.4.1 Complete study population and crude amputation number

Between the period of 2008-2018, 6944 any incident amputations were performed (3505 major amputations, 4335 minor amputations) and 10,569 total amputations in 4580 (65.9%) men and 2372 (34.1%) women. A description of all people undergoing incident amputation over the period is shown in Table 6.1. The diabetes population greater than 17 years of age increased by 29.4% from 143,595 in 2008 to 206,818 in 2018. The crude diabetes prevalence over the 10-year period increased by 2.1% from 5.9% in 2008 to 8.0% of the whole population in 2018. There was a greater prevalence of diabetes in men across the entire period (men 4% vs women 3.2%). The mean age of the population with diabetes over the age of 17 years increased from 65 (±14.7) years to 66.7 (±14.8) years over the period.

The annual number of any incident amputation per year increased from 617 in 2008 to 663 in 2018. The number of incident major amputations decreased from 338 to 290/year and minor amputations increased from 360 to 458/year. This was mirrored in the diabetes population with the incidence of any first-time amputation increasing from 302 to 356/year, major amputation rate decreasing from 154 to 137/year and minor amputation increasing from 198 to 289/year. In the non-diabetes population, the number of total procedures fell between 2008 to 2018 with 315 any incident amputations performed in 2008 and 307 performed in 2018. Major amputation rates decreased from 184 to 153/year and there was a slight increase in minor amputation from 162 to 169/year between 2008 and 2018.

The mean age at first-time amputation over the whole period was 67.9 years (±14.49 years) with a significant difference in the age at amputation between men and women in the total population (men 66.9 ±14.3 years; women 69.9 ±14.6 years , $p<0.01$). The mean age at amputation between genders was significantly different in both those with diabetes (men 67.7 ±12.14 years, women: 69.0 ±13.35 years, $p<0.01$) and without (men 65.8 ±16.71 years, women 70.5 ±15.40 years, $p<0.001$); the variance between the mean age was greater in the non-diabetes population. The was no significant change in the mean age at incident amputation over the period. There was no significant difference in age at amputation between those with (68 ±12.5 years) and without diabetes (67.8 ±16.34 years). Over half (n=3579) of the people undergoing amputation over the entire period had a diagnosis of diabetes. A higher proportion of men undergoing amputation had a diagnosis of diabetes (61.9%) compared to women (45.1%). This was consistent over the period.

Most amputations occurred in older individuals with 62.7% of incident amputations occurring in those aged over 65 years (61.3% diabetes, 64.2% non-diabetes). The male to female ratio of amputations in the diabetes population (3.00 95% CI [2.91-3.08]) was significantly higher than in the non-diabetes population (1.52 [1.46-1.58]). There was an excess of minor amputations in population with diabetes combared to those without with a higher major to minor ratio (1.87 [1.81-1.93] vs 1.04 [0.99-1.08] respectively).

Table 6.1 Description of all patients undergoing incident amputation between 2008-2018 in the population with and without diabetes per year

Characteristics	Total	Men	Women	Diabetes	No Diabetes	Men		Women	
						Diabetes	No diabetes	Diabetes	No diabetes
Year of amputation: 2008									
Number of amputations (%)	617 (100.0)	390 (63.2)	227 (36.8)	302 (48.9)	315 (51.1)	215 (55.1)	175 (44.9)	87 (38.3)	140 (61.7)
Person years (%)	2426841 (100.0)	1172760 (48.3)	1254081 (51.7)	143595 (5.9)	2283246 (94.1)	78592 (6.7)	1094168 (93.3)	65003 (5.2)	1189078 (94.8)
Mean age (years, sd)	67.4 ±14.7	66.4 ±14.3	69.1 ±15.4	67.3 ±13	67.4 ±16.3	67.1 ±12.3	65.5 ±16.4	67.9 ±14.6	69.8 ±15.8
Number of amputations by type									
Major (%)	338 (100.0)	230 (68.0)	108 (32.0)	154 (45.6)	184 (54.4)	111 (48.3)	119 (51.7)	43 (39.8)	65 (60.2)
Minor (%)	360 (100.0)	228 (63.3)	132 (36.7)	198 (55.0)	162 (45.0)	147 (64.5)	81 (35.5)	51 (38.6)	81 (61.4)
Minor to major ratio	1.07	0.99	1.22	1.29	0.88	1.32	0.68	1.19	1.25
Year of amputation: 2009									
Number of amputations (%)	621 (100.0)	389 (62.6)	232 (37.4)	309 (49.8)	312 (50.2)	205 (52.7)	184 (47.3)	104 (44.8)	128 (55.2)
Person years (%)	2442868 (100.0)	1182125 (48.4)	1260743 (51.6)	151174 (6.2)	2291694 (93.8)	83018 (7.0)	1099107 (93.0)	68156 (5.4)	1192587 (94.6)
Mean age (years, sd)	67.8 ±14.8	66.6 ±15.1	69.8 ±14.3	67.5 ±12.6	68.0 ±16.8	66.9 ±11.7	66.2 ±18.1	68.6 ±14.2	70.7 ±14.4
Number of amputations by type									
Major (%)	310 (100.0)	209 (67.4)	101 (32.6)	153 (49.4)	157 (50.6)	100 (47.8)	109 (52.2)	53 (52.5)	48 (47.5)
Minor (%)	372 (100.0)	225 (60.5)	147 (39.5)	205 (55.1)	167 (44.9)	138 (61.3)	87 (38.7)	67 (45.6)	80 (54.4)
Minor to major ratio	1.2	1.08	1.46	1.34	1.06	1.38	0.80	1.26	1.67
Year of amputation: 2010									
Number of amputations (%)	614 (100.0)	404 (65.8)	210 (34.2)	305 (49.7)	309 (50.3)	222 (55.0)	182 (45.0)	83 (39.5)	127 (60.5)
Person years (%)	2455955 (100.0)	1190609 (48.5)	1265346 (51.5)	159327 (6.5)	2296628 (93.5)	87843 (7.4)	1102766 (92.6)	71484 (5.6)	1193862 (94.4)
Mean age (years, sd)	67.5 ±14.0	66.1 ±13.6	70.2 ±14.3	67.3 ±12.2	67.7 ±15.6	65.9 ±11.6	66.4 ±15.7	71.1 ±12.8	69.6 ±15.3
Number of amputations by type									
Major (%)	309 (100.0)	206 (66.7)	103 (33.3)	152 (49.2)	157 (50.8)	105 (51.0)	101 (49.0)	47 (45.6)	56 (54.4)
Minor (%)	362 (100.0)	241 (66.6)	121 (33.4)	201 (55.5)	161 (44.5)	153 (63.5)	88 (36.5)	48 (39.7)	73 (60.3)
Minor to major ratio	1.17	1.17	1.17	1.32	1.03	1.46	0.87	1.02	1.30
Year of amputation: 2011									
Number of amputations (%)	586 (100.0)	384 (65.5)	202 (24.5)	302 (51.5)	284 (48.5)	220 (57.3)	164 (42.7)	82 (40.6)	120 (59.4)
Person years (%)	2470563 (100.0)	1199804 (48.6)	1270759 (51.4)	166820 (6.8)	2303743 (93.2)	92268 (7.7)	1107536 (92.3)	74552 (5.9)	1196207 (94.1)
Mean age (years, sd)	69.1 ±14.6	68.8 ±14.1	69.7 ±15.4	70.2 ±12.1	68 ±16.8	69.6 ±12.0	67.8 ±16.6	71.9 ±12.3	68.3 ±17.1
Number of amputations by type									

Major (%)	328 (100.0)	227 (69.2)	101 (30.8)	168 (51.2)	160 (48.8)	123 (54.2)	104 (45.8)	45 (44.6)	56 (55.4)
Minor (%)	335 (100.0)	220 (65.7)	115 (34.3)	196 (58.5)	139 (41.5)	148 (67.3)	72 (32.7)	48 (41.7)	67 (58.3)
Minor to major ratio	1.02	0.97	1.14	1.17	0.87	1.20	0.69	1.07	1.20
Year of amputation: 2012									
Number of amputations (%)	638 (100.0)	404 (63.3)	234 (36.7)	297 (46.6)	341 (53.4)	227 (56.2)	177 (43.8)	70 (29.9)	164 (70.1)
Person years (%)	2480544 (100.0)	1205263 (48.6)	1275281 (51.4)	173975 (7.0)	2306569 (93.0)	96547 (8.0)	1108716 (92.0)	77428 (6.1)	1197853 (93.9)
Mean age (years, sd)	68.3 ±14.7	66.2 ±14.6	71.9 ±14.1	68.1 ±13.0	68.4 ±16.1	67.7 ±12.7	64.3 ±16.6	69.5 ±13.9	73.2 ±14.1
Number of amputations by type									
Major (%)	348 (100.0)	228 (65.5)	120 (34.5)	176 (50.6)	172 (49.4)	123 (53.9)	105 (46.1)	53 (44.2)	67 (55.8)
Minor (%)	365 (100.0)	230 (63.0)	135 (37.0)	192 (52.6)	173 (47.4)	149 (64.8)	81 (35.2)	43 (31.9)	92 (68.1)
Minor to major ratio	1.05	1.01	1.13	1.09	1.01	1.21	0.77	0.81	1.37
Year of amputation: 2013									
Number of amputations (%)	635 (100.0)	427 (67.2)	208 (32.8)	324 (51.0)	311 (49.0)	241 (56.4)	186 (43.6)	83 (39.9)	125 (60.1)
Person years (%)	2489257 (100.0)	1210989 (48.6)	1278268 (51.4)	180024 (7.2)	2309233 (92.8)	100150(8.3)	1110839 (91.7)	79874 (6.2)	1198394 (93.8)
Mean age (years, sd)	68.1 ±14.4	67.1 ±14.4	70.3 ±14.3	68 ±12.2	68.2 ±16.4	67.4 ±12.3	66.7 ±16.7	69.8 ±12.1	70.5 ±15.7
Number of amputations by type									
Major (%)	302 (100.0)	212 (70.2)	90 (29.8)	146 (48.3)	156 (51.7)	108 (50.9)	104 (49.1)	38 (42.2)	52 (57.8)
Minor (%)	405 (100.0)	274 (67.7)	131 (32.3)	237 (58.5)	168 (41.5)	184 (67.2)	90 (32.8)	53 (40.5)	78 (59.5)
Minor to major ratio	1.34	1.29	1.46	1.62	1.08	1.70	0.87	1.39	1.50
Year of amputation: 2014									
Number of amputations (%)	624 (100.0)	424 (67.9)	200 (32.1)	343 (55.0)	281 (45.0)	257 (60.6)	167 (39.4)	86 (43.0)	114 (57.0)
Person years (%)	2500687 (100.0)	1218052 (48.7)	1282635 (51.3)	186599 (7.5)	2314088 (92.5)	103920(8.5)	1114132 (91.5)	82679 (6.4)	1199956 (93.6)
Mean age (years, sd)	68.8 ±13.9	67.6 ±13.7	71.4 ±13.9	69 ±12.4	68.5 ±15.5	68.6 ±12.0	65.9 ±15.8	69.9 ±13.6	72.4 ±14.2
Number of amputations by type									
Major (%)	313 (100.0)	227 (72.5)	86 (27.5)	169 (54.0)	144 (46.0)	130 (57.3)	97 (42.7)	39 (45.3)	47 (54.7)
Minor (%)	398 (100.0)	272 (68.3)	126 (31.7)	236 (59.3)	162 (40.7)	183 (67.3)	89 (32.7)	53 (42.1)	73 (57.9)
Minor to major ratio	1.27	1.20	1.47	1.40	1.13	1.41	0.92	1.36	1.55
Year of amputation: 2015									
Number of amputations (%)	667 (100.0)	442 (66.3)	225 (33.7)	353 (52.9)	314 (47.1)	255 (57.7)	187 (42.3)	98 (43.6)	127 (56.4)
Person years (%)	2507896 (100.0)	1222426 (48.7)	1285470 (51.3)	191726 (7.6)	2316170 (92.4)	107026(8.8)	1115400 (91.2)	84700 (6.6)	1200770 (93.4)
Mean age (years, sd)	67.3 ±14.9	66.8 ±15.0	68.3 ±14.7	67.2 ±13.0	67.4 ±16.8	67.2 ±12.8	66.4 ±17.4	67.3 ±13.5	69.2 ±15.6

Number of amputations by type									
Major (%)	325 (100.0)	223 (68.6)	102 (31.4)	154 (47.4)	171 (52.6)	106 (47.5)	117 (52.5)	48 (47.1)	54 (52.9)
Minor (%)	444 (100.0)	290 (65.3)	154 (34.7)	277 (62.4)	167 (37.6)	192 (66.2)	98 (33.8)	85 (55.2)	69 (44.8)
Minor to major ratio	1.37	1.30	1.51	1.80	0.98	1.81	0.84	1.77	1.28
Year of amputation: 2016									
Number of amputations (%)	682 (100.0)	449 (65.8)	233 (34.2)	360 (52.8)	322 (47.2)	258 (57.5)	191 (42.5)	102 (43.8)	131 (56.2)
Person years (%)	2521273 (100.0)	1230462 (48.8)	1290811 (51.2)	197084 (7.8)	2324189 (92.2)	110009(8.9)	1120453 (91.1)	87075 (6.7)	1203736 (93.3)
Mean age (years, sd)	68.4 ±14.4	67.7 ±14.3	69.8 ±14.5	68.4 ±12.6	68.5 ±16.2	68.5 ±12.0	66.7 ±16.8	68.1 ±13.8	71.1 ±15.0
Number of amputations by type									
Major (%)	339 (100.0)	219 (64.6)	120 (35.4)	170 (50.1)	169 (49.9)	118 (53.9)	101 (46.1)	52 (43.3)	68 (56.7)
Minor (%)	463 (100.0)	317 (68.5)	146 (31.5)	283 (61.1)	180 (38.9)	206 (65.0)	111 (35.0)	77 (52.7)	69 (47.3)
Minor to major ratio	1.37	1.45	1.22	1.66	1.07	1.75	1.10	1.48	1.01
Year of amputation: 2017									
Number of amputations (%)	597 (100.0)	408 (68.3)	189 (31.7)	317 (53.1)	280 (46.9)	246 (60.3)	162 (39.7)	71 (37.6)	118 (62.4)
Person years (%)	2531863 (100.0)	1235960 (48.8)	1295903 (51.2)	200167 (7.9)	2331696 (92.1)	111864(9.1)	1124096 (90.9)	88303 (6.8)	1207600 (93.2)
Mean age (years, sd)	67.9 ±14.6	67.4 ±14.1	68.8 ±15.6	68.0 ±12.2	67.7 ±16.9	68.2 ±12.0	66.2 ±16.7	67.2 ±12.9	69.8 ±16.9
Number of amputations by type									
Major (%)	303 (100.0)	210 (69.3)	93 (30.7)	157 (51.8)	146 (48.2)	119 (56.7)	91 (43.3)	38 (40.9)	55 (59.1)
Minor (%)	373 (100.0)	260 (69.7)	113 (30.3)	221 (59.2)	152 (40.8)	179 (68.8)	81 (31.2)	42 (37.2)	71 (62.8)
Minor to major ratio	1.23	1.24	1.22	1.41	1.04	1.50	0.89	1.11	1.29
Year of amputation: 2018									
Number of amputations (%)	663 (100.0)	453 (68.3)	210 (31.7)	356 (53.7)	307 (46.3)	271 (59.8)	182 (40.2)	85 (40.5)	125 (59.5)
Person years (%)	2543119 (100.0)	1242148 (48.8)	1300971 (51.2)	203302 (8.0)	2339817 (92.0)	113659(9.2)	1128489 (90.8)	89643 (6.9)	1211328 (93.1)
Mean age (years, sd)	66.7 ±14.3	65.3 ±14.1	69.7 ±14.2	67.5 ±12.0	65.8 ±16.5	67.3 ±12.0	62.4 ±16.4	68.2 ±12.3	70.9 ±15.3
Number of amputations by type									
Major (%)	290 (100.0)	195 (67.2)	95 (32.8)	137 (47.2)	153 (52.8)	97 (49.7)	98 (50.3)	40 (42.1)	55 (57.9)
Minor (%)	458 (100.0)	319 (69.7)	139 (30.3)	289 (63.1)	169 (36.9)	225 (70.5)	94 (29.5)	64 (46.0)	75 (54.0)
Minor to major ratio	1.58	1.64	1.46	2.11	1.10	2.32	0.96	1.60	1.36

Only incident amputation counted.

6.4.2 Incidence rate of any, major, minor and total lower limb amputation in the population with and without diabetes and the influence of diabetes on risk of amputation.

The age and sex standardised amputation rate (AR) as well as the relative risk of amputation in the population with diabetes compared to those without diabetes for each calendar year for incident and total amputations are shown in Table 6.2, and Figures 6.1 and 6.2. The results of the fully adjusted Poisson models are shown in Table 6.3.

In the total population the rate of any incident amputation for the whole period was 2.5 [95% CI 2.5-2.6] /10 000 PY and any total amputation was 3.9 [3.8-3.9]/10 000 PY (Table 6.2). The rate of incident major amputation for the whole period (1.3 [1.2-1.3]/10 000 PY) was lower than that of incident minor amputation (1.6 [1.5-1.6]/10 000 PY). The rate of total major amputation (1.6 [1.5-1.6]/10 000 PY) was also lower than the rate of total minor amputation (2.3 [2.2-2.3]/10 000 PY). For any, major and minor incident and total amputation the rate for the whole period was higher for men.

Over the 11-year period, when controlling for population changes in age and gender there was no significant change in the rate of incident any and minor amputation in the whole population. There was a statistically significant rate reduction for incident major amputation reducing from 1.5 [1.3-1.6]/10 000 PY in 2008 to 1.1 [1.0-1.1]/10 000 PY in 2018. When stratified by gender the rate change was only significant for men.

6.4.2.1 Diabetes related amputation

In the diabetes population the rate of incident amputation for the whole period was 12.8 [12.2-13.4]/10 000 PY and total amputation was 22.8 [22.4-23.2]/10 000 PY, 5.1 and 5.9 times higher than the rate in the whole population respectively. People with diabetes underwent a greater number of incident amputations and were more likely to undergo multiple amputations per year. As in the total population, the rate of incident major amputation (5.8 [5.4-6.2]/10 000 PY) was lower than that of incident minor amputation (9.5 [7.8-11.5]/10 000 PY). This was also true for total amputations performed with a greater difference between the two rates (major: 7.3 [7.0-7.5] vs minor: 15.5 [14.9-16.1]/10 000 PY). As in the whole population for all, major and minor incident and total amputation the rate for the whole period was higher for men.

Over the 11-year period there was no statistically significant change in the standardised rate of any incident or total minor amputations per year in the diabetes population despite the increase in the crude rate and total number of people undergoing amputation. Poisson regression analysis identified a significant decrease in incidence of all and major incident amputation after adjustment for age and sex (Table 6.3). When stratified by gender the rate change was significant for women.

The incidence of incident and total all, major and minor amputation was significantly higher within the male population. The age standardised rate of any amputation type was 2-3-fold higher among men compared to women, in both those with and without diabetes. This was consistent over the period and the overall rate of change did not differ significantly between genders in all and minor amputation. There was a rate reduction in the number of incident major amputations in the diabetes population from 6.9 [5.5-8.5]/10 000 PY in 2008 to 4.9 [5.4-6.2]/ 10 000 PY in 2018 corresponding to a 30% relative risk reduction between the two years (Figure 6.1b). When stratified by gender the rate of change was greater in women but significant for both genders. The rate of minor amputation in the diabetes population remained stable over the period.

When stratified by age, the incident any amputation rate ratio was highest among individuals between 75-84 years for both men and women with diabetes when compared to the age of 17-44 years. When the analysis was stratified by gender the incident rate ratio was higher for men within the age range (men 2.78 [95%CI: 2.25-3.42]: women 2.44 [95%CI: 1.77-3.37]). When controlling for age and year the risk of any incident lower extremity amputation attributed to diabetes was higher in men (8.53 [7.22-10.1]) compared to women (5.39 [4.38-6.62]). This was more marked for minor amputations (men:13.30 [10.89-16.24]: women 6.28 [4.96-7.94]) than major amputations (men 6.55 [5.59-7.68]: women 6.43 [5.19-7.96]).

6.4.2.2 Non-diabetes related amputations

In the non-diabetes population the rate of any incident amputation for the whole period was 1.4 [1.4-1.5]/10 000 PY and any total amputation was 1.9 [1.9-2.0]/10 000 PY, 5.9 and 12 times lower than the rate in the diabetes population respectively. The non-diabetes population underwent less incident amputations and were less likely to undergo multiple amputations each year than the diabetes population. The rate of incident major (0.8 [0.7-0.8]/10 000 PY) and minor (0.8 [0.7-0.8]/10 000 PY) amputation was the same. This was also true for the total major and minor amputations performed (0.9 [0.9-1.0]/10 000 PY). As in the total and diabetes population for all, major and minor incident and total amputation the rate for the whole period was higher for men.

As within the diabetes population there was an increase in the crude number of people undergoing incident amputations and in the total number of procedures performed over the 11 years. There was no significant change in the age-sex standardised amputation rate for incident or total any, major or minor amputation. Poisson regression analysis showed no significant decrease in incidence of amputation per year after adjustment for age and sex. Despite no reduction in the total incident major amputation rate, in the gender stratified analysis there was a significant reduction in the rate of major amputations in men without diabetes from 0.9 [0.8-1.1]/ 10 000 PY in 2008 to 0.7 [0.6-0.8]/ 10 000 population years in 2018. A 22.2% relative risk reduction.

The incidence of any amputation type was significantly higher in men compared to women. This was consistent over the period. In the gender specific analysis, when stratified by age the incident rate ratio was highest among individuals 85 years and above for both men and women. The incident rate ratio was higher in women in this age group when controlling for year (men 24.22 [20.11-29.18]: women 28.91 [23.14-36.13]). Within the Poisson models age had a significantly greater effect on incident rate ratio for both genders in those without diabetes compared to those with diabetes.

Table 6.2 Incident and Total Amputation rate per 10 000 population and relative risk of amputation in the Welsh population with and without diabetes between 2008-2018

Calendar year	Incident amputation rate [95% CI]/ 10 000 PY			Relative risk [95% CI]	Total amputation rate [95% CI]/ 10 000 person years			Relative risk [95% CI]
	ARt	ARd	ARn	RR	ARt	ARd	ARn	RR
Any amputation - Total Population								
2008	2.7 [2.5-2.9]	16.1 [13.3-19.1]	1.5 [1.4-1.7]	11 [10.8-11.2]	3.9 [3.6-4.1]	24.8 [21.6-28.4]	2.0 [1.8-2.2]	12.4 [12.2-12.6]
2009	2.7 [2.4-2.9]	14.6 [12.4-17.0]	1.5 [1.4-1.7]	10.1 [9.9-10.3]	3.8 [3.6-4.1]	23.6 [20.8-26.6]	1.9 [1.7-2.1]	12.5 [12.3-12.6]
2010	2.6 [2.4-2.8]	13.5 [11.5-15.6]	1.5 [1.3-1.7]	9.5 [9.3-9.7]	3.6 [3.4-3.9]	23.4 [20.6-26.5]	1.9 [1.7-2.0]	12.7 [12.5-12.8]
2011	2.4 [2.2-2.6]	11.5 [9.7-13.5]	1.4 [1.2-1.5]	8.7 [8.5-9.0]	3.5 [3.3-3.8]	21.3 [18.6-24.1]	1.7 [1.5-1.9]	12.6 [12.4-12.7]
2012	2.6 [2.4-2.8]	12.5 [10.4-14.7]	1.6 [1.5-1.8]	8.1 [7.9-8.3]	3.7 [3.5-4.0]	22.3 [19.6-25.2]	1.9 [1.7-2.0]	12.0 [11.9-12.2]
2013	2.6 [2.4-2.8]	11.9 [10.3-13.8]	1.5 [1.3-1.6]	8.5 [8.3-8.7]	3.8 [3.5-4.0]	20.8 [18.5-23.3]	1.8 [1.6-2.0]	11.4 [11.3-11.6]
2014	2.5 [2.3-2.7]	12.2 [10.4-14.2]	1.3 [1.2-1.5]	9.8 [9.6-10.0]	3.9 [3.7-4.2]	22.0 [19.6-24.6]	1.8 [1.6-1.9]	12.5 [12.4-12.7]
2015	2.6 [2.4-2.8]	13.9 [11.9-16.1]	1.5 [1.3-1.6]	10.1 [9.9-10.3]	4.2 [3.9-4.4]	25.2 [22.5-28.1]	1.9 [1.8-2.1]	13.0 [12.8-13.1]
2016	2.6 [2.4-2.8]	12.5 [10.8-14.4]	1.5 [1.3-1.7]	8.9 [8.7-9.1]	4.3 [4.1-4.6]	24.5 [21.9-27.2]	2.0 [1.8-2.2]	12.4 [12.3-12.6]
2017	2.3 [2.1-2.5]	10.6 [9.0-12.3]	1.3 [1.1-1.4]	8.7 [8.5-8.9]	3.7 [3.5-4.0]	20.0 [17.9-22.3]	1.7 [1.5-1.9]	11.8 [11.6-11.9]
2018	2.5 [2.3-2.7]	12.3 [10.5-14.2]	1.4 [1.2-1.5]	9.3 [8.5-8.9]	4.0 [3.8-4.2]	23.3 [20.7-26.1]	1.8 [1.6-2.0]	13.0 [12.8-13.1]
Whole period	2.5 [2.5-2.6]	12.8 [12.2-13.4]	1.4 [1.4-1.5]	9.1 [8.9-9.3]	3.9 [3.8-3.9]	22.8 [22.4-23.2]	1.9 [1.9-2.0]	12.3 [12.0-12.5]
Men								
2008	3.5 [3.2-3.9]	20.4 [16.8-24.5]	1.8 [1.6-2.1]	11.9 [11.7-12.2]	5.3 [4.9-5.8]	33.2 [28.5-38.2]	2.4 [2.1-2.8]	13.7 [13.4-14.0]
2009	3.4 [3.1-3.8]	16.9 [14.0-20.0]	1.9 [1.6-2.2]	9.4 [9.1-9.6]	5.2 [4.8-5.6]	29.7 [25.6-34.1]	2.4 [2.1-2.8]	12.2 [11.9-12.4]
2010	3.5 [3.2-3.9]	19.5 [16.1-23.3]	1.9 [1.6-2.2]	11.2 [11.0-11.4]	5.1 [4.7-5.5]	33.2 [28.4-38.4]	2.4 [2.1-2.7]	14.0 [13.7-14.2]
2011	3.3 [3.0-3.6]	15.7 [12.9-18.7]	1.7 [1.4-2.0]	9.9 [9.6-10.1]	5.0 [4.6-5.4]	27.9 [24.0-32.2]	2.1 [1.9-2.4]	13.1 [12.8-13.3]
2012	3.4 [3.1-3.7]	17.9 [14.6-21.5]	1.7 [1.5-2.0]	10.8 [10.5-11.0]	5.0 [4.6-5.4]	29.4 [25.4-33.7]	2.1 [1.8-2.4]	14.1 [13.7-14.3]
2013	3.5 [3.2-3.9]	17.1 [14.2-20.3]	1.8 [1.6-2.1]	9.8 [9.6-10.1]	5.5 [5.1-5.9]	30.7 [26.8-35.0]	2.3 [2.0-2.7]	13.1 [12.8-13.3]
2014	3.4 [3.1-3.8]	17.1 [14.1-20.4]	1.6 [1.4-1.9]	11.1 [10.8-11.3]	5.8 [5.4-6.2]	33.0 [28.9-37.4]	2.2 [1.9-2.5]	15.0 [14.8-15.3]
2015	3.5 [3.2-3.9]	18.7 [15.2-22.4]	1.8 [1.6-2.1]	11 [10.8-11.3]	5.9 [5.5-6.4]	31.7 [27.6-36.1]	2.7 [2.3-3.0]	12.0 [11.7-12.2]
2016	3.5 [3.2-3.9]	15.7 [13.3-18.4]	1.8 [1.6-2.1]	8.9 [8.8-9.2]	6.1 [5.7-6.6]	32.8 [28.8-37.0]	2.6 [2.3-2.9]	12.8 [12.5-13.1]
2017	3.2 [2.9-3.5]	14.8 [12.3-17.6]	1.5 [1.3-1.8]	10.1 [9.9-10.4]	5.5 [5.1-6.0]	29.1 [25.7-32.8]	2.1 [1.8-2.4]	13.8 [13.5-14.0]
2018	3.5 [3.2-3.9]	17.2 [14.3-20.3]	1.7 [1.4-1.9]	10.6 [10.3-10.8]	5.8 [5.4-6.3]	32.9 [28.7-37.4]	2.3 [2.0-2.6]	14.3 [14.0-14.5]
Whole period	3.4 [3.3-3.5]	17.3 [16.3-18.2]	1.8 [1.7-1.9]	9.6 [9.4-9.8]	5.5 [5.4-5.6]	31.2 [30.8-31.5]	2.3 [2.2-2.4]	13.4 [13.2-13.6]
Women								
2008	1.9 [1.6-2.1]	11.9 [7.9-16.7]	1.3 [1.1-1.5]	9.8 [9.4-10.3]	2.5 [2.2-2.8]	16.9 [12.4-22.1]	1.6 [1.4-1.9]	10.5 [10.3-10.8]
2009	1.9	12.5	1.2	11.1	2.5	17.9	1.4	12.9

	[1.7-2.2]	[9.2-16.3]	[1.0-1.4]	[10.8-11.5]	[2.2-2.8]	[14.1-22.2]	[1.2-1.6]	[12.5-13.1]
2010	1.7	7.8	1.2	6.9	2.3	14.2	1.4	10.4
	[1.5-1.9]	[5.8-10.1]	[1.0-1.4]	[6.6-7.3]	[2.0-2.5]	11.0-17.7]	[1.1-1.6]	[10.1-10.6]
2011	1.6	7.6	1.1	7.2	2.2	15.0	1.3	11.8
	[1.4-1.9]	[5.4-10.2]	[0.9-1.3]	[6.9-7.6]	[1.9-2.5]	[11.4-19.0]	[1.1-1.5]	[11.6-12.1]
2012	1.9	7.4	1.5	5.3	2.5	15.6	1.6	9.5
	[1.6-2.1]	[5.1-10.1]	[1.3-1.7]	[4.9-5.7]	[2.3-2.8]	[12.0-19.6]	[1.4-1.9]	[9.2-9.7]
2013	1.6	7.1	1.1	6.6	2.1	11.4	1.3	8.6
	[1.4-1.9]	[5.3-9.1]	[0.9-1.3]	[6.3-6.9]	[1.9-2.4]	[9.0-14.1]	[1.1-1.6]	[8.3-8.8]
2014	1.5	7.6	1.0	7.9	2.2	11.6	1.3	8.6
	[1.3-1.8]	[5.6-10.0]	[0.8-1.2]	[7.6-8.3]	[1.9-2.4]	[9.1-14.5]	[1.1-1.6]	[8.3-8.9]
2015	1.7	9.4	1.1	8.8	2.5	19.0	1.3	15.0
	[1.5-2.0]	[7.2-12.0]	[0.9-1.3]	[8.5-9.1]	[2.3-2.8]	[15.6-22.9]	[1.1-1.5]	[14.7-15.2]
2016	1.8	9.5	1.2	8.7	2.6	16.6	1.4	11.8
	[1.6-2.0]	[7.2-12.2]	[1.0-1.4]	[8.4-9.0]	[2.3-2.9]	[13.5-20.1]	[1.2-1.6]	[11.5-12.0]
2017	1.4	6.6	1.0	6.7	2.0	11.5	1.3	8.7
	[1.2-1.6]	[4.7-8.9]	[0.9-1.2]	[6.4-7.1]	[1.8-2.3]	[8.9-14.4]	[1.1-1.5]	[8.4-8.9]
2018	1.6	7.7	1.1	7.5	2.2	14.2	1.3	10.7
	[1.4-1.8]	[5.5-10.2]	[0.9-1.3]	[7.1-7.8]	[2.0-2.5]	[11.2-17.7]	[1.1-1.6]	[10.5-11.0]
Whole period	1.5	8.4	1.0	8.4	2.3	14.9	1.4	10.8
	[1.4-1.6]	[7.6-9.2]	[0.9-1.1]	[8.2-8.6]	[2.2-2.4]	[14.7-15.1]	[1.3-1.5]	[10.6-11.1]
Major amputation - Total Population								
calendar year								
2008	1.5	6.9	0.9	7.9	1.7	8.4	1.0	8.0
	[1.3-1.6]	[5.5-8.5]	[0.8-1.1]	[7.7-8.2]	[1.6-1.9]	[6.9-10.1]	[0.9-1.2]	[7.7-8.3]
2009	1.3	7.0	0.8	9.5	1.6	8.2	0.9	9.0
	[1.2-1.5]	[5.5-8.6]	[0.7-0.9]	[9.3-9.8]	[1.4-1.8]	[6.6-9.9]	[0.8-1.1]	[8.7-9.3]
2010	1.3	5.9	0.8	8.0	1.6	7.6	0.9	8.2
	[1.2-1.5]	[4.8-7.1]	[0.7-0.9]	[7.7-8.2]	[1.4-1.7]	[6.2-9.1]	[0.8-1.1]	[7.9-8.5]
2011	1.4	5.7	0.8	7.6	1.6	7.3	0.9	7.9
	[1.2-1.5]	[4.7-6.9]	[0.7-0.9]	[7.3-7.8]	[1.5-1.8]	[6.0-8.7]	[0.8-1.1]	[7.6-8.1]
2012	1.4	6.4	0.8	8.2	1.7	8.4	0.9	9.0
	[1.3-1.6]	[5.2-7.8]	[0.7-1.0]	[7.9-8.5]	[1.6-1.9]	[7.0-10.0]	[0.8-1.1]	[8.7-9.2]
2013	1.2	5.4	0.7	7.7	1.5	7.1	0.9	8.0
	[1.1-1.4]	[4.3-6.6]	[0.6-0.9]	[7.4-7.9]	[1.4-1.7]	[5.8-8.5]	[0.8-1.0]	[7.7-8.3]
2014	1.2	5.3	0.7	8.1	1.6	6.6	0.9	7.7
	[1.1-1.4]	[4.2-6.4]	[0.6-0.8]	[7.8-8.4]	[1.4-1.7]	[5.4-7.8]	[0.7-1.0]	[7.4-7.9]
2015	1.3	5.6	0.8	7.4	1.6	6.9	0.9	7.3
	[1.1-1.4]	[4.4-6.9]	[0.7-0.9]	[7.1-7.7]	[1.4-1.7]	[5.7-8.3]	[0.8-1.1]	[7.0-7.6]
2016	1.3	6.0	0.8	8.1	1.6	7.1	0.9	7.7
	[1.2-1.5]	[4.8-7.4]	[0.7-0.9]	[7.8-8.4]	[1.4-1.7]	[5.8-8.5]	[0.8-1.1]	[7.4-7.9]
2017	1.2	5.2	0.7	8.1	1.5	6.7	0.8	8.1
	[1.0-1.3]	[4.0-6.4]	[0.6-0.8]	[7.8-8.4]	[1.3-1.6]	[5.5-8.0]	[0.7-1.0]	[7.8-8.4]
2018	1.1	4.9	0.7	7.6	1.4	6.4	0.8	7.7
	[1.0-1.2]	[3.8-6.2]	[0.6-0.8]	[7.3-7.8]	[1.3-1.5]	[5.1-7.8]	[0.7-1.0]	[7.4-7.9]
Whole Period	1.3	5.8	0.8	7.3	1.6	7.3	0.9	8.2
	[1.2-1.3]	[5.4-6.2]	[0.7-0.8]	[7.1-7.5]	[1.5-1.6]	[7.0-7.5]	[0.8-1.0]	[8.0-8.4]
Men								
2008	2.1	9.7	1.2	8.2	2.5	12.1	1.4	8.4
	[1.8-2.4]	[7.3-12.4]	[1.0-1.5]	[7.9-8.6]	[2.2-2.8]	[9.5-15.1]	[1.2-1.7]	[8.1-8.8]
2009	1.9	7.9	1.1	7.3	2.3	9.6	1.3	7.2
	[1.6-2.1]	[6.0-10.0]	[0.9-1.4]	[7.0-7.7]	[2.0-2.6]	[7.6-11.9]	[1.1-1.6]	[6.8-7.3]
2010	1.8	7.9	1.0	8.0	2.2	10.7	1.3	8.3
	[1.6-2.1]	[6.1-10.0]	[0.8-1.3]	[7.7-8.3]	[2.0-2.5]	[8.2-13.4]	[1.1-1.5]	[8.0-8.7]
2011	2.0	8.1	1.1	7.9	2.3	10.0	1.3	7.8
	[1.7-2.2]	[6.3-10.2]	[0.9-1.3]	[7.6-8.3]	[2.0-2.6]	[7.8-12.5]	[1.1-1.5]	[7.5-8.2]
2012	1.9	7.2	1.0	7.1	2.4	9.7	1.2	8.2
	[1.7-2.2]	[5.9-8.8]	[0.9-1.3]	[6.8-7.3]	[2.1-2.7]	[8.2-11.5]	[1.0-1.4]	[7.9-8.6]
2013	1.8	7.7	1.0	7.9	2.2	9.4	1.3	7.3

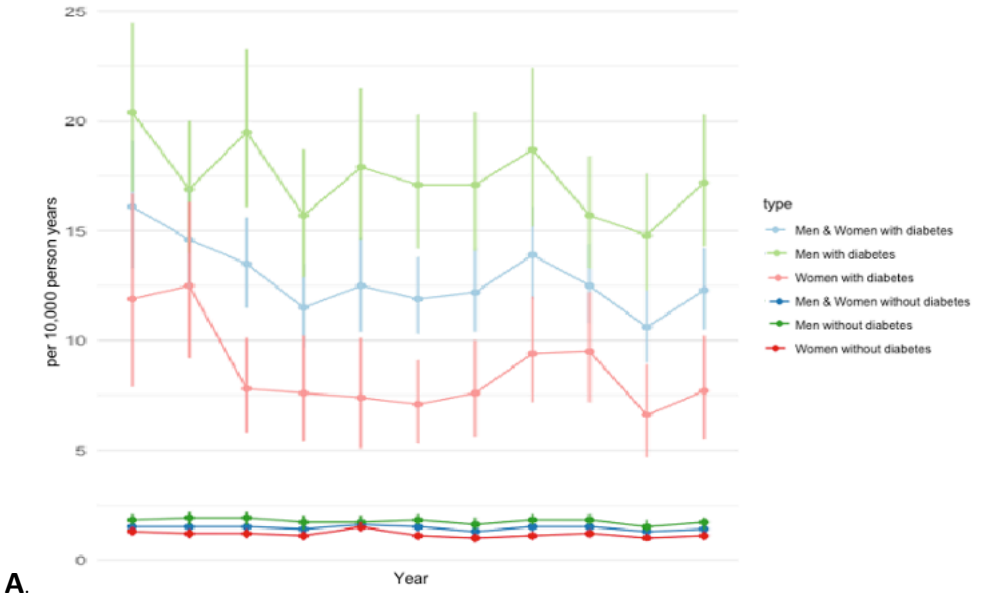
	[1.5-2.0]	[5.8-9.9]	[0.8-1.2]	[7.6-8.3]	[1.9-2.5]	[7.4-11.7]	[1.1-1.5]	[7.0-7.7]
2014	1.8	7.5	1.0	8.2	2.3	9.6	1.2	8.2
	[1.6-2.1]	[5.9-9.4]	[0.8-1.2]	[7.9-8.6]	[2.0-2.6]	[7.8-11.6]	[1.0-1.4]	[7.9-8.6]
2015	1.8	5.9	1.1	5.4	2.2	7.7	1.4	5.6
	[1.6-2.0]	[4.5-7.5]	[0.9-1.4]	[5.1-5.7]	[2.0-2.5]	[6.2-9.4]	[1.1-1.6]	[5.3-5.9]
2016	1.7	7.7	1.0	8.4	2.1	8.9	1.2	7.4
	[1.5-2.0]	[5.8-9.9]	[0.8-1.2]	[8.1-8.8]	[1.9-2.4]	[6.9-11.1]	[1.0-1.4]	[7.1-7.8]
2017	1.6	6.8	0.9	8.2	2.1	8.8	1.1	8.0
	[1.4-1.9]	[5.2-8.7]	[0.7-1.1]	[7.9-8.6]	[1.9-2.4]	[7.1-10.8]	[0.9-1.3]	[7.7-8.3]
2018	1.5	6.5	0.9	7.4	2.0	8.1	1.1	7.3
	[1.3-1.7]	[4.7-8.5]	[0.7-1.1]	[7.1-7.8]	[1.7-2.2]	[6.2-10.2]	[0.9-1.3]	[6.9-7.4]
Whole period	1.8	7.5	1.0	7.5	2.2	9.5	1.3	7.8
	[1.7-1.9]	[6.9-8.0]	[1.0-1.1]	[7.3-7.7]	[2.1-2.3]	[9.0-10.1]	[1.2-1.3]	[7.6-8.0]
Women								
2008	0.9	4.2	0.6	7.3	1.0	4.9	0.7	7.3
	[0.7-1.1]	[2.7-6.1]	[0.5-0.8]	[6.9-7.8]	[0.8-1.2]	[3.3-6.8]	[0.5-0.8]	[6.9-7.8]
2009	0.8	6.1	0.4	14.7	0.9	6.8	0.5	13.3
	[0.7-1.0]	[3.9-8.8]	[0.3-0.6]	[14.2-15.2]	[0.8-1.1]	[4.5-9.5]	[0.4-0.7]	[12.8-13.7]
2010	0.8	4.0	0.5	7.9	1.0	4.7	0.6	8.1
	[0.7-1.0]	[2.8-5.4]	[0.4-0.7]	[7.4-8.3]	[0.8-1.2]	[3.4-6.2]	[0.4-0.7]	[7.6-8.5]
2011	0.8	3.4	0.5	6.8	1.0	4.7	0.6	8.1
	[0.7-1.0]	[2.4-4.8]	[0.4-0.7]	[6.4-7.3]	[0.8-1.2]	[3.4-6.2]	[0.4-0.7]	[7.6-8.5]
2012	0.9	5.7	0.6	10.0	1.1	7.1	0.7	10.4
	[0.8-1.1]	[3.6-8.2]	[0.5-0.8]	[9.5-10.4]	[0.9-1.3]	[4.8-9.9]	[0.5-0.9]	[9.9-10.8]
2013	0.7	3.2	0.5	7.1	0.9	4.9	0.5	9.4
	[0.6-0.9]	[2.1-4.5]	[0.3-0.6]	[6.6-7.5]	[0.7-1.1]	[3.4-6.8]	[0.4-0.7]	[8.9-9.8]
2014	0.7	3.1	0.4	7.8	0.8	3.7	0.6	6.7
	[0.5-0.8]	[1.9-4.6]	[0.3-0.6]	[7.2-8.3]	[0.7-1.0]	[2.4-5.3]	[0.4-0.7]	[6.3-7.2]
2015	0.8	5.3	0.5	11.7	0.9	6.2	0.5	11.5
	[0.6-1.0]	[3.4-7.6]	[0.4-0.6]	[11.3-12.2]	[0.8-1.1]	[4.3-8.6]	[0.4-0.7]	[11.1-11.9]
2016	0.9	4.4	0.6	7.6	1.1	5.4	0.7	8.2
	[0.8-1.1]	[2.8-6.3]	[0.5-0.8]	[7.2-8.1]	[0.9-1.3]	[3.8-7.4]	[0.5-0.8]	[7.9-8.6]
2017	0.7	3.6	0.5	7.8	0.9	4.7	0.6	8.2
	[0.6-0.9]	[2.1-5.4]	[0.4-0.6]	[7.3-8.4]	[0.7-1.0]	[3.1-6.6]	[0.4-0.7]	[7.9-8.6]
2018	0.7	3.5	0.5	7.8	0.9	4.7	0.6	8.5
	[0.6-0.9]	[2.2-5.1]	[0.4-0.6]	[7.3-8.3]	[0.7-1.0]	[3.1-6.7]	[0.4-0.7]	[8.2-8.9]
Whole Period	0.7	4.0	0.4	10.0	1.0	5.3	0.6	8.8
	[0.7-0.7]	[3.6-4.6]	[0.4-0.5]	[9.6-10.5]	[1.0-1.1]	[4.9-5.7]	[0.5-0.6]	[8.4-9.2]
Minor amputation - Total population								
2008	1.6	11.7	0.8	15.7	2.1	16.4	1.0	17.2
	[1.4-1.7]	[9.1-14.6]	[0.7-0.9]	[15.4-16.0]	[1.9-2.3]	[13.6-19.6]	[0.8-1.1]	[16.9-17.6]
2009	1.6	9.9	0.8	12.8	2.2	15.5	1.0	15.7
	[1.4-1.8]	[8.1-12.0]	[0.7-1.0]	[12.5-13.0]	[2.0-2.4]	[13.1-18.0]	[0.9-1.1]	[15.4-16.0]
2010	1.5	9.7	0.8	13.2	2.0	15.8	0.9	17.0
	[1.4-1.7]	[7.9-11.7]	[0.7-0.9]	[13.0-13.5]	[1.9-2.2]	[13.3-18.6]	[0.8-1.1]	[16.7-17.4]
2011	1.4	8.4	0.7	13.3	1.9	14.0	0.8	18.2
	[1.2-1.5]	[6.7-10.3]	[0.6-0.8]	[13.0-13.6]	[1.8-2.1]	[11.7-16.5]	[0.7-0.9]	[17.9-18.6]
2012	1.5	8.8	0.8	11.4	2.0	13.9	0.9	15.1
	[1.3-1.6]	[7.0-10.7]	[0.7-1.0]	[11.1-11.4]	[1.8-2.2]	[11.7-16.4]	[0.8-1.1]	[14.9-15.8]
2013	1.6	8.5	0.8	11.2	2.2	13.7	0.9	14.7
	[1.5-1.8]	[7.1-10.0]	[0.7-0.9]	[10.9-12.9]	[2.1-2.4]	[11.8-15.8]	[0.8-1.1]	[14.5-15.2]
2014	1.6	9.1	0.8	12.7	2.4	15.4	0.9	17.1
	[1.4-1.7]	[7.4-10.9]	[0.6-0.9]	[12.4-16.0]	[2.2-2.6]	[13.4-17.7]	[0.8-1.0]	[16.8-17.5]
2015	1.7	11.4	0.8	15.7	2.6	18.3	1.0	18.3
	[1.6-1.9]	[9.5-13.5]	[0.7-0.9]	[15.5-16.2]	[2.4-2.8]	[16.0-20.8]	[0.9-1.1]	[18.0-18.7]
2016	1.8	9.8	0.8	12.4	2.7	17.4	1.0	16.6
	[1.6-2.0]	[8.3-11.4]	[0.7-1.0]	[12.2-12.6]	[2.5-2.9]	[15.2-19.7]	[0.9-1.2]	[16.2-16.9]
2017	1.4	7.7	0.7	11.7	2.2	13.4	0.9	15.4
	[1.3-1.6]	[6.3-9.2]	[0.6-0.8]	[11.5-12.0]	[2.1-2.4]	[11.6-15.2]	[0.7-1.0]	[15.0-15.7]

2018	1.7	10.0	0.8	13.8	2.6	17.0	1.0	17.4
	[1.6-1.9]	[8.4-11.8]	[0.6-0.9]	[13.6-14.0]	[2.4-2.8]	[14.7-19.4]	[0.8-1.1]	[17.0-17.7]
Whole Period	1.6	9.5	0.8	11.9	2.3	15.5	0.9	16.6
	[1.5-1.6]	[7.8-11.5]	[0.7-0.8]	[11.8-12.0]	[2.2-2.3]	[14.9-16.1]	[0.9-1.0]	[16.0-17.1]
Men								
2008	2.0	14.8	0.8	18.8	2.8	21.1	1.0	21.6
	[1.8-2.3]	[11.6-18.5]	[0.7-1.0]	[18.5-19.2]	[2.5-3.1]	[17.3-25.2]	[0.8-1.2]	[21.3-21.9]
2009	2.0	11.6	0.9	13.7	2.9	20.0	1.1	18.4
	[1.7-2.3]	[9.2-14.4]	[0.7-1.1]	[13.4-14.0]	[2.6-3.3]	[16.5-23.9]	[0.9-1.3]	[18.1-18.8]
2010	2.1	14.6	0.9	17.5	2.9	22.5	1.1	20.8
	[1.8-2.4]	[11.5-18.1]	[0.7-1.1]	[17.1-17.8]	[2.6-3.2]	[18.4-27.1]	[0.9-1.3]	[20.5-21.2]
2011	1.9	12.0	0.7	17.6	2.7	17.9	0.9	21.0
	[1.6-2.2]	[9.3-15.1]	[0.6-0.9]	[17.2-17.9]	[2.4-3.0]	[14.7-21.4]	[0.7-1.1]	[20.7-21.4]
2012	1.9	13.4	0.8	18.0	2.6	19.7	0.9	22.2
	[1.7-2.2]	[10.3-16.9]	[0.6-1.0]	[17.6-18.3]	[2.4-2.9]	[16.0-23.7]	[0.7-1.1]	[22.8-23.5]
2013	2.3	12.7	0.9	15.1	3.3	21.4	1.1	20.1
	[2.0-2.5]	[10.4-15.4]	[0.7-1.1]	[14.8-15.4]	[3.0-3.6]	[18.0-25.0]	[0.9-1.3]	[19..8-21.4]
2014	2.2	13.4	0.9	16.4	3.5	23.4	1.0	22.9
	[2.0-2.5]	[10.5-16.6]	[0.7-1.1]	[16.1-16.8]	[3.2-3.8]	[19.8-27.4]	[0.8-1.2]	[22.6-23.1]
2015	2.3	15.3	1.0	17.4	3.7	24.1	1.3	18.7
	[2.1-2.6]	[12.0-18.9]	[0.8-1.2]	[17.1-17.7]	[3.4-4.0]	[20.3-28.2]	[1.1-1.5]	[18.4-19.1]
2016	2.5	12.0	1.1	11.8	4.0	23.9	1.4	17.5
	[2.2-2.8]	[10.0-14.2]	[0.9-1.3]	[11.5-12.0]	[3.7-4.4]	[20.4-27.6]	[1.1-1.6]	[17.2-17.8]
2017	2.0	11.8	0.8	16.4	3.4	20.3	1.0	20.2
	[1.8-2.3]	[9.4-14.4]	[0.6-1.0]	[16.1-16.7]	[3.1-3.7]	[17.4-23.4]	[0.8-1.2]	[19.9-20.8]
2018	2.5	14.7	0.9	17.6	3.9	24.8	1.2	20.9
	[2.2-2.8]	[11.9-17.7]	[0.7-1.1]	[17.3-17.9]	[3.6-4.2]	[21.1-28.8]	[1.0-1.4]	[20.6-21.1]
Whole Period	2.2	13.3	0.9	14.8	3.3	21.7	1.1	19.9
	[2.1-2.2]	[12.5-14.2]	[0.8-0.9]	[14.6-15.0]	[3.2-3.3]	[21.3-22.2]	[1.0-1.1]	[19.4-20.3]
Women								
2008	1.1	8.7	0.7	12.5	1.5	12.0	0.9	12.8
	[0.9-1.3]	[4.9-13.4]	[0.6-0.9]	[11.9-13.0]	[1.3-1.7]	[7.9-17.0]	[0.8-1.1]	[12.4-13.2]
2009	1.2	8.3	0.8	11.8	1.6	11.1	0.9	12.6
	[1.0-1.4]	[5.7-11.5]	[0.6-0.9]	[11.4-12.2]	[1.3-1.8]	[8.1-14.6]	[0.7-1.1]	[12.2-13.0]
2010	1.0	5.1	0.7	8.0	1.3	9.5	0.8	12.1
	[0.8-1.2]	[3.3-7.3]	[0.5-0.8]	[7.6-8.5]	[1.1-1.5]	[6.7-12.8]	[0.6-1.0]	[11.6-12.5]
2011	0.9	5.0	0.6	8.6	1.2	10.3	0.7	14.9
	[0.8-1.1]	[3.0-7.4]	[0.5-0.8]	[8.1-9.1]	[1.0-1.4]	[7.0-14.1]	[0.5-0.9]	[14.5-15.3]
2012	1.1	4.4	0.8	5.5	1.4	8.4	1.0	8.8
	[0.9-1.3]	[2.6-6.5]	[0.7-1.0]	[5.0-6.0]	[1.2-1.7]	[5.8-11.5]	[0.8-1.2]	[8.3-9.2]
2013	1.0	4.5	0.7	6.6	1.3	6.4	0.8	8.0
	[0.9-1.2]	[3.0-6.2]	[0.6-0.9]	[6.2-7.0]	[1.1-1.5]	[4.6-8.6]	[0.6-1.0]	[7.5-8.4]
2014	1.0	5.0	0.6	8.1	1.3	7.9	0.8	9.9
	[0.8-1.2]	[3.3-7.0]	[0.5-0.8]	[7.6-8.5]	[1.1-1.5]	[5.8-10.4]	[0.6-1.0]	[9.6-10.4]
2015	1.2	7.7	0.6	13.4	1.6	12.8	0.7	17.6
	[1.0-1.4]	[5.8-10.0]	[0.5-0.8]	[13.0-13.7]	[1.4-1.8]	[10.1-15.9]	[0.6-0.9]	[16.9-17.8]
2016	1.1	7.7	0.6	13.5	1.5	11.2	0.7	15.0
	[0.9-1.3]	[5.5-10.3]	[0.5-0.8]	[13.1-13.9]	[1.3-1.7]	[8.6-14.2]	[0.6-0.9]	[14.5-15.3]
2017	0.9	3.8	0.6	6.5	1.1	6.8	0.7	9.2
	[0.7-1.0]	[2.5-5.5]	[0.5-0.8]	[6.1-7.0]	[1.0-1.3]	[4.8-9.2]	[0.6-0.9]	[8.8-9.7]
2018	1.0	5.6	0.6	9.1	1.4	9.5	0.8	12.3
	[0.9-1.2]	[3.8-7.8]	[0.5-0.8]	[8.7-9.6]	[1.2-1.6]	[7.0-12.5]	[0.6-1.0]	[11.7-12.8]
Whole Period	0.9	5.8	0.6	9.7	1.4	9.6	0.8	12.0
	[0.9-1.0]	[5.1-6.5]	[0.6-0.6]	[9.3-10.0]	[1.4-1.5]	[9.1-10.2]	[0.8-0.9]	[11.6-12.5]

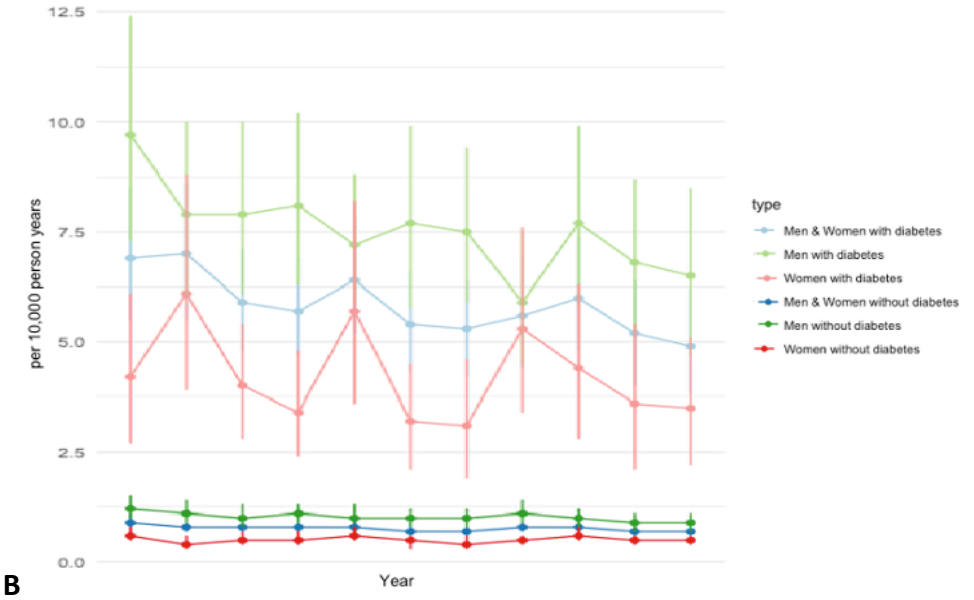
Age-gender and gender rates standardised to Welsh population ONS midyear estimate 2013.

ARt- Amputation rate total population, ARd - Amputation rate diabetic population, ARn - Amputation rate non diabetic population, RR- relative risk of amputation, diabetic population compared to non-diabetic population.

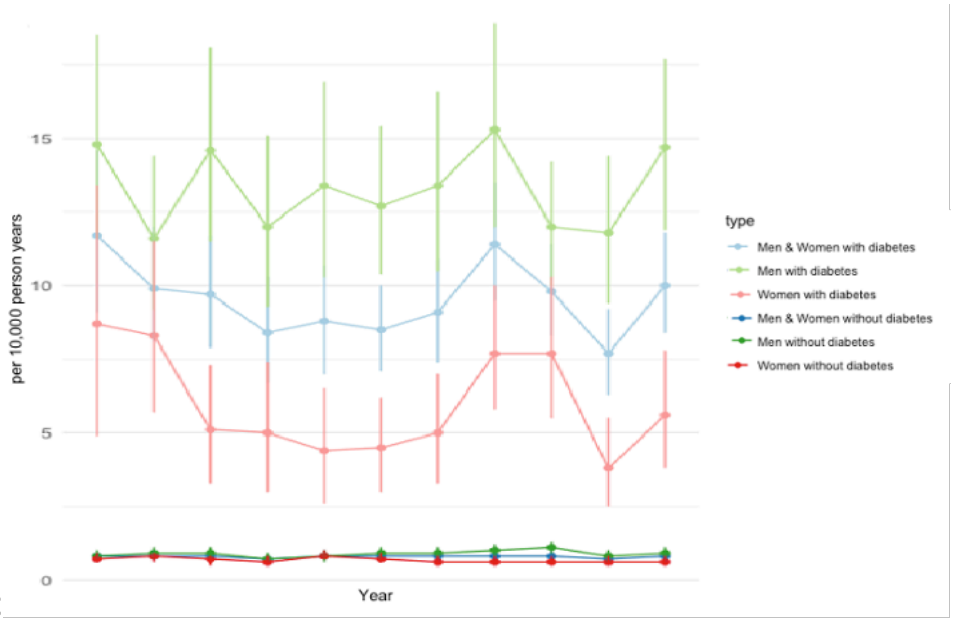
Figure 6.1 Time trend of age-sex standardised incident amputation rate of (A) any amputation (B) major amputation (C) minor amputation with 95% CI



A.

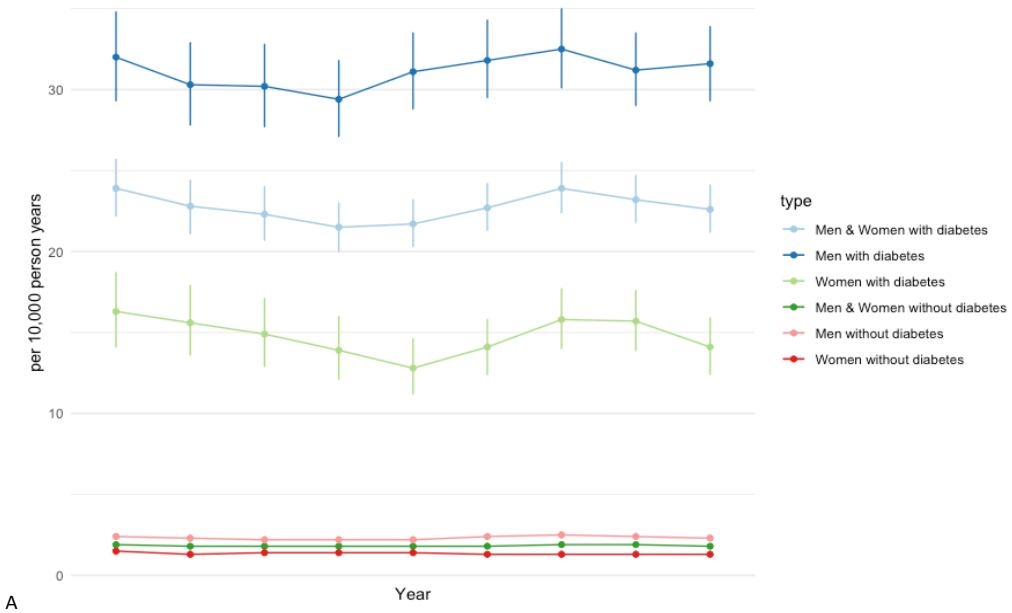


B

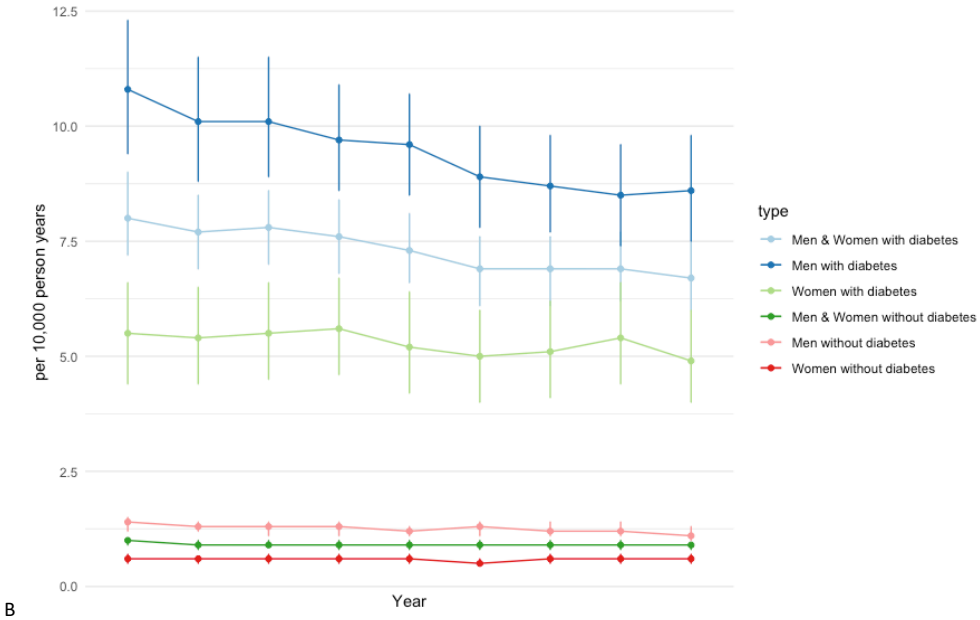


C

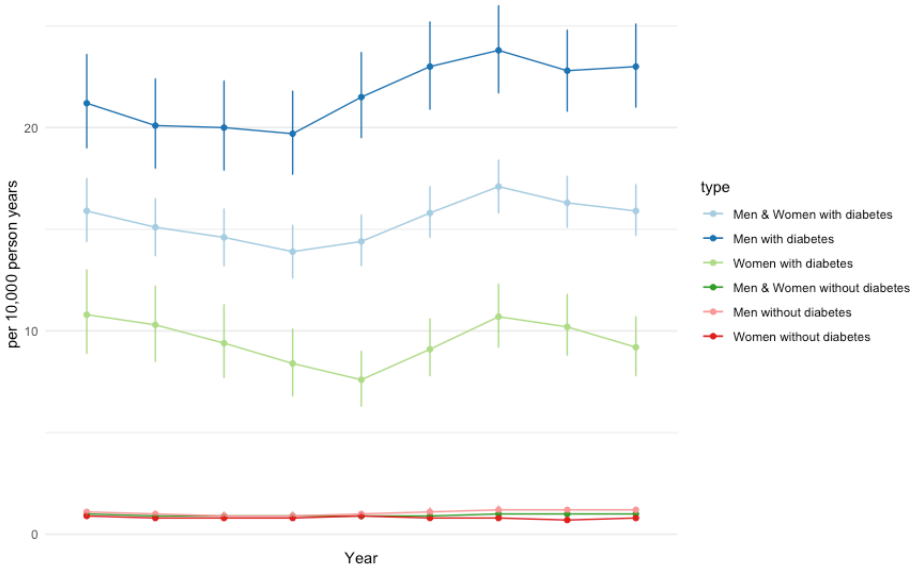
Figure 6.2 Time trend of age-sex standardised total amputation rate of (A) any amputation (B) major amputation (C) minor amputation with 95% CI



A



B



C

Table 6.3 Incident rate ratios (IRR) of incident lower- extremity amputation per year adjusted for age, sex and presence of diabetes

Independent Variable	Total	Total		Total		Men		Women	
		Men	Women	Diabetes	No Diabetes	Diabetes	No Diabetes	Diabetes	No Diabetes
	IRR [95% CI]	IRR [95% CI]	IRR [95% CI]	IRR [95% CI]	IRR [95% CI]	IRR [95% CI]	IRR [95% CI]	IRR [95% CI]	IRR [95% CI]
Any amputation									
Year[a]	0.98 [0.98-1.00]	0.99 [0.97-1.01]	0.97 [0.95-1.00]	**0.98 [0.97-0.99]***	0.99 [0.98-1.00]	0.99 [0.98-1.00]	0.99 [0.98-1.01]	**0.96 [0.94-0.99]***	0.98 [0.97-1.00]
Diabetes(Y vs N)	**7.27 [6.35-8.33]***	**8.53 [7.22-10.1]***	**5.39 [4.38-6.62]***	-		-	-	-	-
Gender (M vs W)	**1.95 [1.74-2.19]***	-	-	**2.2 [2.02-2.40]***	**1.76 [1.65-1.88]***	-	-	-	-
Age (years)[b]									
45-64	**6.65 [5.68-7.78]***	**3.99 [3.17-5.02]***	**4.09 [2.99-5.59]***	**2.31 [1.92-2.76]***	**3.25 [2.90-3.66]***	**2.42 [1.96-2.99]***	**3.18 [2.76-3.66]***	**2.09 [1.49-2.91]***	**3.44 [2.95-4.01]***
65-74	**6.65 [5.68-7.78]***	**5.78 [4.78-7.00]***	**8.35 [6.53-10.68]***	**2.29 [1.92-2.72]***	**8.54 [7.64-9.55]***	**2.40 [1.96-2.95]***	**7.45 [6.59-8.42]***	**2.05 [1.52-2.77]***	**10.76 [9.07-12.77]***
74-85	**9.64 [7.97-11.65]***	**8.18 [6.38-10.49]***	**12.63 [9.56-16.70]***	**2.67 [2.23-3.20]***	**16.96 [15.27-18.8]***	**2.78 [2.25-3.42]***	**15.36 [13.69-17.24]***	**2.44 [1.77-3.37]***	**20.17 [17.01-2.39]***
85+	**11.42 [8.81-14.79]***	**10.08 [7.23-14.05]***	**13.97 [9.52-20.50]***	**2.29 [1.83-2.86]***	**25.56 [22.1-29.60]***	**2.74 [2.16-3.47]***	**24.22 [20.11-29.18]***	**1.63 [1.07-2.48]***	**28.91 [23.14-36.13]***
Major amputation									
Year[a]	**0.97 [0.95-0.99]***	**0.97 [0.95-0.99]***	0.97 [0.95-1.00]	**0.96 [0.95-0.97]***	0.98 [0.97-1.00]	**0.96 [0.95-0.98]***	**0.98 [0.96-0.99]***	**0.95 [0.93-0.98]***	0.99 [0.97-1.01]
Diabetes(Y vs N)	**6.51 [5.73-7.41]***	**6.55 [5.59-7.68]***	**6.43 [5.19-7.96]***	-	-	-	-	-	-
Gender (M vs W)	**2.19 [1.94-2.46]***	-	-	**2.01 [1.83-2.22]***	**2.35 [2.15-2.58]***	-	-	-	-
Age (years)[b]									
45-64	**4.3 [3.54-5.24]***	**4.55 [3.61-5.75]***	**3.72 [2.59-5.36]***	**3.32 [2.45-4.48]***	**3.23 [2.76-3.77]***	**3.98 [2.96-5.35]***	**3.41 [2.84-4.09]***	**2.44 [1.41-4.21]***	**2.83 [2.10-3.81]***
65-74	**7.55 [6.39-9.93]***	**7.45 [6.13-9.06]***	**7.81 [5.68-10.74]***	**3.66 [2.70-4.95]***	**8.41 [7.16-9.88]***	**4.36 [3.23-5.89]***	**8.13 [6.75-9.78]***	**2.75 [1.61-4.69]***	**9.00 [6.48-12.48]***
74-85	**11.13 [9.12-13.59]***	**11.04 [8.62-14.14]***	**11.3 [8.02-15.91]***	**4.22 [3.10-5.74]***	**17.11 [14.55-20.1]***	**5.12 [3.77-6.94]***	**17.02 [14.01-20.68]***	**3.02 [1.74-5.24]***	**17.31 [12.71-23.56]***
85+	**13.33 [10.28-17.27]***	**12.93 [9.34-17.92]***	**13.71 [8.89-21.17]***	**3.68 [2.60-5.21]***	**25.96 [21.4-31.46]***	**4.87 [3.32-7.12]***	**24.28 [19.33-30.48]***	**2.32 [1.33-4.06]***	**27.93 [19.76-39.48]***
Minor amputation									
Year[a]	1.00 [0.98-1.02]	1.01 [0.98-1.03]	0.98 [0.96-1.01]	1.00 [0.99-1.02]	1.00 [0.98-1.01]	1.01 [0.99-1.02]	1.01 [0.98-1.03]	0.99 [0.96-1.02]	0.98 [0.96-1.00]
Diabetes(Y vs N)	**10.15 [8.63-1.19]***	**13.3 [10.89-16.24]***	**6.28 [4.96-7.94]***	-	-	-	-	-	-
Gender (M vs W)	**1.91 [1.67-2.19]***			**2.40 [2.14-2.69]***	**1.49 [1.35-1.65]***	-	-	-	-
Age (years)[b]									
45-64	**4.08 [3.16-5.28]***	**3.67 [2.70-4.99]***	**4.54 [3.12-6.62]***	**1.99 [1.60-2.47]***	**3.39 [2.82-4.07]***	**2.03 [1.56-2.63]***	**3.02 [2.37-3.85]***	**1.91 [1.30-2.79]***	**4.18 [3.40-5.16]***
65-74	**5.91 [4.67-7.49]***	**4.77 [3.57-6.36]***	**8.23 [5.85-11.58]***	**1.80 [1.46-2.22]***	**9.49 [7.90-11.40]***	**1.88 [1.45-2.44]***	**7.78 [6.30-9.61]***	**1.58 [1.11-2.26]**	**12.97 [1.01-1.67]***
74-85	**8.03 [6.16-10.48]***	**6.08 [4.35-8.51]***	**12.6 [8.80-18.05]***	**2.06 [1.66-2.57]***	**18.04 [15.1-21.49]***	**2.08 [1.59-2.72]***	**14.84 [11.92-18.48]***	**2.02 [1.41-2.89]***	**24.24 [19.54-30.07]***
85+	**8.98 [6.55-12.3]***	**7.32 [4.78-11.21]***	**12.49 [8.27-18.87]***	**1.81 [1.43-2.30]***	**25.34 [20.4-31.46]***	**1.95 [1.47-2.59]***	**25.76 [18.94-35.03]***	**1.56 [1.05-2.31]**	**28.32 [21.92-36.58]***

[a]IRR per 1 year increment. [b]Reference category 17-44 years. *statistically significant p<0.05. IRR- Incidence Rate Ratio

6.4.2.3 Relative risk of amputation caused by diabetes

For the whole observation period the age-sex standardised amputation rate for incident any amputations was 9.1-fold higher [8.9-9.3] in the diabetes population compared to the non-diabetes population. When stratified by gender the relative risk of incident any amputation in the diabetes population was higher for men (9.6 [9.4-9.8]) than women (8.4 [8.2-8.6]). When stratified by age categories the relative risk of amputation in those with diabetes compared to those without diabetes was greatest amongst those aged 25-44 years (22.1 [21.9-22.3]) and when stratified by gender the risk was greater in women in this age category (23.4 [23.0-23.8]) than men (21.5 [21.2-21.7]).

For major amputation the risk of incident amputation in people with diabetes was 7.3 fold higher [7.1-7.5] than in those without diabetes. When stratified by gender the relative risk of amputation associated with diabetes was higher for women (10.0 [9.6-9.5]) than men (7.5 [7.3-7.7]). When stratified by age the risk caused by a history of diabetes was highest amongst those aged 45-64 years for men (13.7 [13.6-13.9]) and those aged 25-45 years for women (19.9[19.4-20.4]).

For minor amputations the risk of incident amputation in people with diabetes was 11.9 fold higher [11.8 -1.01] than in those without diabetes. When stratified by gender the relative risk of amputation in the diabetes population was higher for men (14.8 [14.6-15.0]). When stratified by age the risk of amputation associated with a history of diabetes was greatest amongst those aged 24-45 (38.7 [38.4- 8.9]) and higher in men within this age category (40.6 [40.3-40.9) than women (35.1 [34.7-35.5]). The relative risk of amputation associated with diabetes was higher than that seen for major amputations.

There was no clear change in the relative risk of amputation associated with a history of diabetes over the period apart from for major amputation. When comparing the first and last four-year periods of observation (Table 6.4), 2008-2011 and 2015-2018, the relative risk of any incident amputation among the diabetes population compared to the non-diabetes population did not decrease significantly for either gender. When stratified by age there was, however, a significant reduction in the risk of amputation for those with diabetes compared to those without diabetes in those aged 17-44 years and 75-84 years for both genders, ages

45-64 years for men and 85+ years for women. There was a significant increase of 29.8% in relative risk compared to the non-diabetic population for women aged 45-64 years, increasing from 14.4 [14.1-14.7] in the 2008-2011 period to 20.5 [20.3-20.8] in the 2015-2018 period.

Table 6.4 Relative risk of incident amputation among the population with diabetes compared to the population without diabetes during first four and last four years of observation period

	Relative risk [95% CI]	
	2008-2011	2015-2018
Men by age group		
17-44	18.8 [18.4-19.2]	15.3 [14.9-15.7]
45-64	20.0 [19.8-20.2]	17.5 [17.3-17.7]
65-74	7.0 [6.8-7.2]	8.1 [7.9-8.3]
75-84	4.5 [4.3-4.7]	3.9 [3.7-4.1]
85+	2.6 [2.3-2.9]	2.5 [2.2-2.8]
All	10.6 [10.5-10.7]	10.2 [10.1-10.3]
Women by age group		
17-44	29.8 [29.2-30.3]	17.7 [17.1-18.3]
45-64	14.4 [14.1-14.7]	20.5 [20.3-20.8]
65-74	5.2 [4.9-5.4]	6.0 [5.8-6.3]
75-84	4.6 [4.3-4.8]	2.5 [2.2-2.7]
85+	2.7 [2.4-3.1]	1.1 [0.7-1.5]
All	8.8 [8.7-9.0]	8.0 [7.8-8.1]

CI- Confidence interval

6.4.2.4 Major-Minor amputation ratio

When looking at the rolling three-year periods, the major-minor amputation ratio for all incident amputations increased significantly from 1.1 [1.1-1.2] in 2008-2010 to 1.4 [1.3-15] in the 2016-2018 period (Table 6.5). The ratio increased significantly in the total male population, the total diabetic population and the male diabetic population. The greatest change was seen in the male diabetic population with a rise from 1.4 [1.3-1.5] at the beginning of the period to 1.8 [1.7-2.0]. There was no significant change in the whole female population, the non-diabetic population or in women with or without diabetes. There was a decrease in the major- minor amputation ratio for women without diabetes from 1.4 [1.2-1.6] at the start of the period to 1.2 [1.1-1.4] by the end although this change was not significant.

Table 6.5 Major -minor amputation ratio for incident amputation over 3 year rolling periods with 95% CI

	Total	Men	Women	Diabetes	No Diabetes	Men		Women	
	[95% CI]					Diabetes	No diabetes	Diabetes	No diabetes
2008-2010	1.1	1.1	1.3	1.3	1.0	1.4	0.8	1.2	1.4
	[1.1-1.2]	[1.0-1.2]	[1.2-1.4]	[1.2-1.4]	[0.9-1.1]	[1.3-1.5]	[0.7-0.9]	[1.0-1.4]	[1.2-1.6]
2009-2011	1.1	1.1	1.3	1.3	1.0	1.3	0.8	1.1	1.4
	[1.1-1.2]	[1.0-1.2]	[1.1-1.4]	[1.2-1.4]	[0.9-1.1]	[1.2-1.5]	[0.7-0.9]	[1.0-1.3]	[1.2-1.6]
2010-2012	1.1	1.0	1.1	1.2	1.0	1.3	0.8	1.0	1.3
	[1.0-1.1]	[1.0-1.1]	[1.0-1.3]	[1.1-1.3]	[0.9-1.1]	[1.2-1.4]	[0.7-0.9]	[0.8-1.1]	[1.1-1.5]
2011-2013	1.1	1.1	1.2	1.3	1.0	1.4	0.8	1.1	1.4
	[1.1-1.2]	[1.0-1.2]	[1.1-1.4]	[1.2-1.4]	[0.9-1.1]	[1.2-1.5]	[0.7-0.9]	[0.9-1.2]	[1.2-1.5]
2012-2014	1.2	1.2	1.3	1.4	1.1	1.4	0.8	1.1	1.5
	[1.1-1.3]	[1.1-1.2]	[1.2-1.5]	[1.3-1.5]	[1.0-1.2]	[1.3-1.6]	[0.7-1.0]	[1.0-1.3]	[1.3-1.7]
2013-2015	1.3	1.3	1.5	1.6	1.1	1.6	0.9	1.5	1.4
	[1.3-1.4]	[1.2-1.4]	[1.3-1.6]	[1.5-1.7]	[1.0-1.2]	[1.5-1.8]	[0.8-1.0]	[1.3-1.8]	[1.3-1.6]
2014-2016	1.3	1.3	1.4	1.6	1.1	1.6	0.9	1.5	1.2
	[1.3-1.4]	[1.2-1.4]	[1.3-1.5]	[1.5-1.7]	[1.0-1.1]	[1.5-1.8]	[0.8-1.1]	[1.3-1.8]	[1.1-1.4]
2015-2017	1.3	1.3	1.3	1.6	1.0	1.7	0.9	1.5	1.2
	[1.3-1.4]	[1.2-1.4]	[1.2-1.4]	[1.5-1.7]	[0.9-1.1]	[1.5-1.8]	[0.8-1.1]	[1.3-1.7]	[1.0-1.4]
2016-2018	1.4	1.4	1.3	1.7	1.1	1.8	1.0	1.4	1.2
	[1.3-1.5]	[1.3-1.5]	[1.2-1.4]	[1.6-1.8]	[1.0-1.2]	[1.7-2.0]	[0.9-1.1]	[1.2-1.6]	[1.1-1.4]

[95% CI]

6.4.3 The incidence of major lower limb amputation across health boards and the influence of diabetes on risk of amputation

6.4.3.1 Incident amputation rate stratified by Health Board

Over the 11-year period the greatest crude number of any, major and minor incident amputations were performed within Health Board (HB) 1 for the whole population. The lowest crude number of any, major and minor incident amputations were performed in HB7 for the whole, diabetes and non-diabetes populations. The age standardised incident any, major and minor amputation rate was highest for the whole population in HB1 at 3.5 [3.3-3.7], 1.9 [1.7-2.0] and 2.2 [1.7-2.0]/10 000 PY respectively (Figures 6.3-6.5). For any and major amputations the amputation rate was lowest in HB3, at 2.0 [1.9-2.1] and 0.8 [0.8-0.9]/10 000 PY, a 1.8x and 2.4x variance between the highest and lowest rates for all and major amputations respectively. For minor amputation the rate was lowest in HB4, at 1.3 [1.2-1.4]/10 000 PY, a 1.7x variance.

As in the whole population, the age standardised rate for all, major and minor incident amputation was highest in HB1 for the non-diabetes population at 1.9 [1.8-2.1], 1.0 [0.9-1.2] and 1.0 [0.9-1.1]/10 000 PY respectively. The rate of incident any amputation was lowest in HB3 and HB7 at 1.2 [1.0-1.4]/10 000 PY, 1.6x lower than the HB with the highest rate. For major amputation the rate was lowest in HB2, HB3, and HB7 at 0.6 [0.5-0.7]/10 000 PY, 1.7x lower than the highest rate. The rate for minor amputation was lowest in HB6 at 0.6 [0.5-0.7]/10 000 PY, 1.7x lower than the highest rate.

As in the whole population analysis, amputation rates in the diabetes population in every HB and for every amputation type were considerably higher than that in the non-diabetes population. In the population with diabetes the incident any, major and minor amputation rate was highest in HB1 at 21.3 [19.6-23.1], 11.0 [9.8-12.4] and 15.9 [14.4-17.4]/10 000 PY respectively. However, the rates from HB1 were less of an outlier within the diabetes population with HB7 having a comparable incident any amputation rate at 21.2 [16.9-26.1]/10 000 PY and HB7 having a similar minor amputation rate of 15.2 [11.5-19.3]/10 000 PY. As for the whole population HB3 had the lowest rates of any and major amputations at 14.4 [13.0-15.9] and 4.4 [3.7-5.3]/10 000 PY respectively, giving a 1.5x and 2.5x variance in rates between

the highest and lowest HB rates. For minor amputation the rate was lowest in HB4 with 9.8 [8.5-11.3]/10 000 PY, 1.6x lower than the rate in HB1 and HB7.

Figure 6.3 incident Any Amputation rate per 10 000 PY in the whole, non-diabetes and diabetes population by Health Board between 2008-2018.

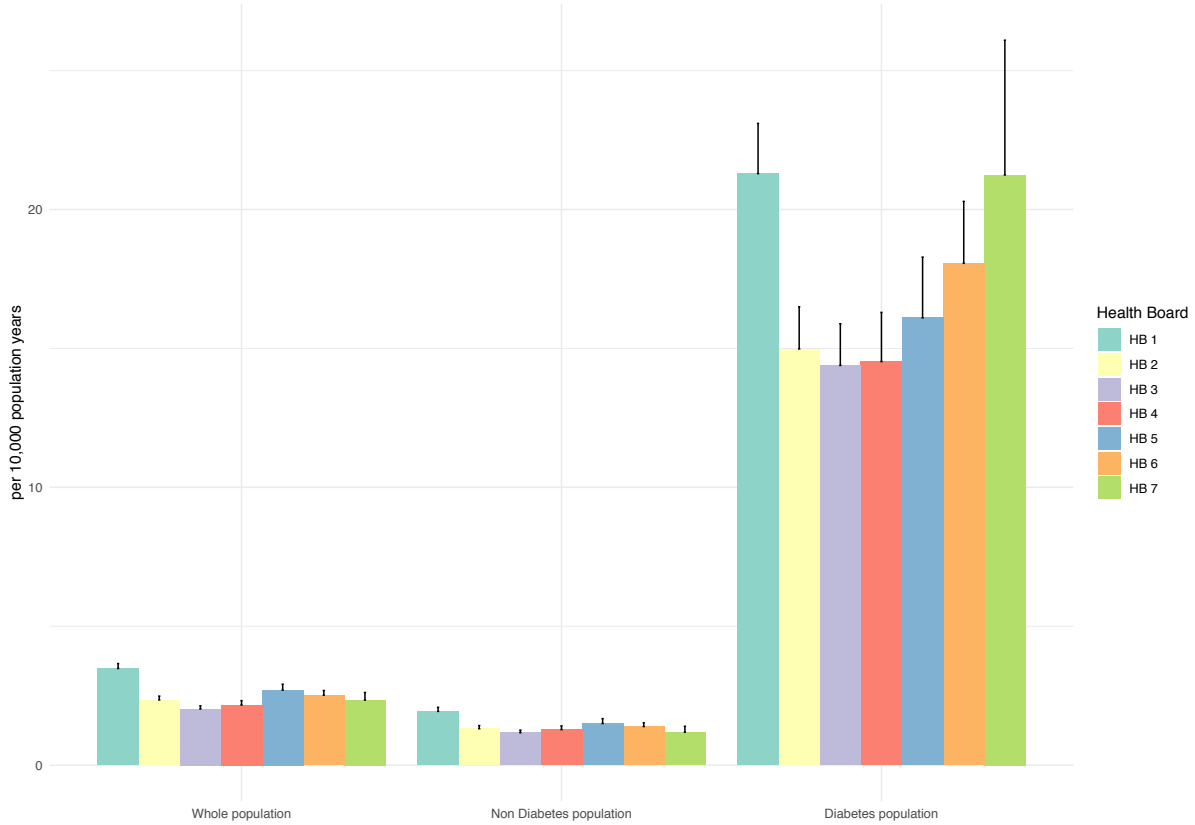


Figure 6.4 Incident Major Amputation rate per 10 000 PY whole, non-diabetes and diabetes population by Health Board between 2008-2018

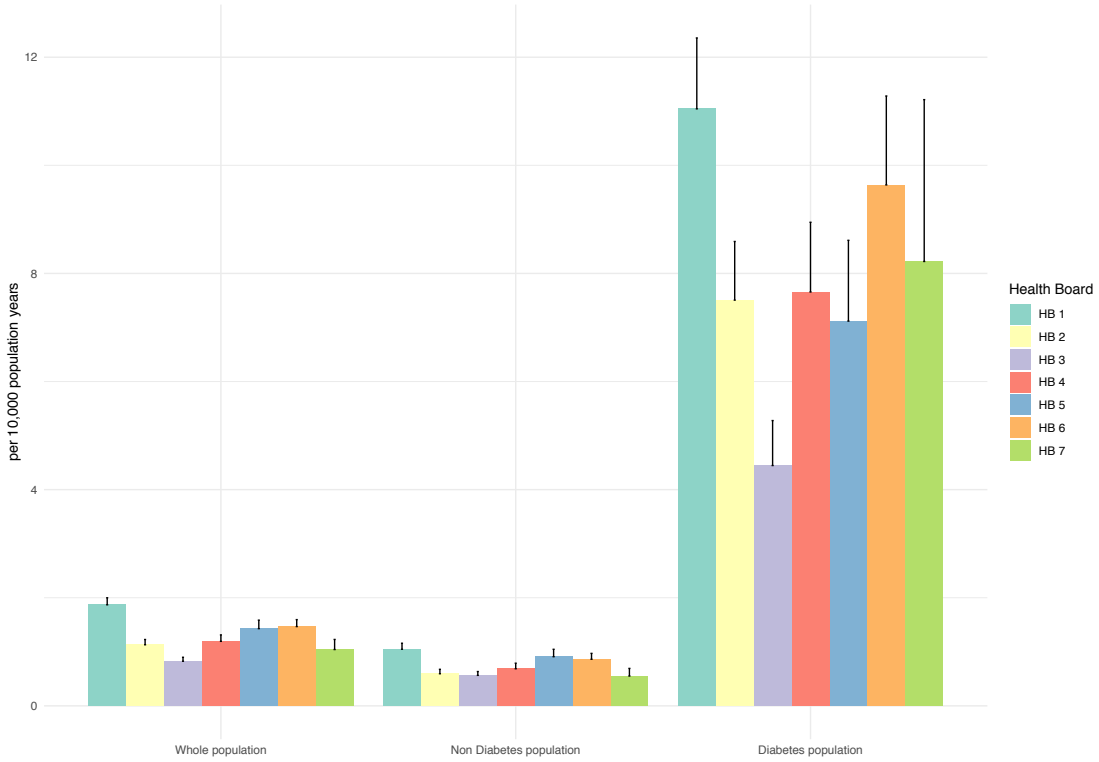
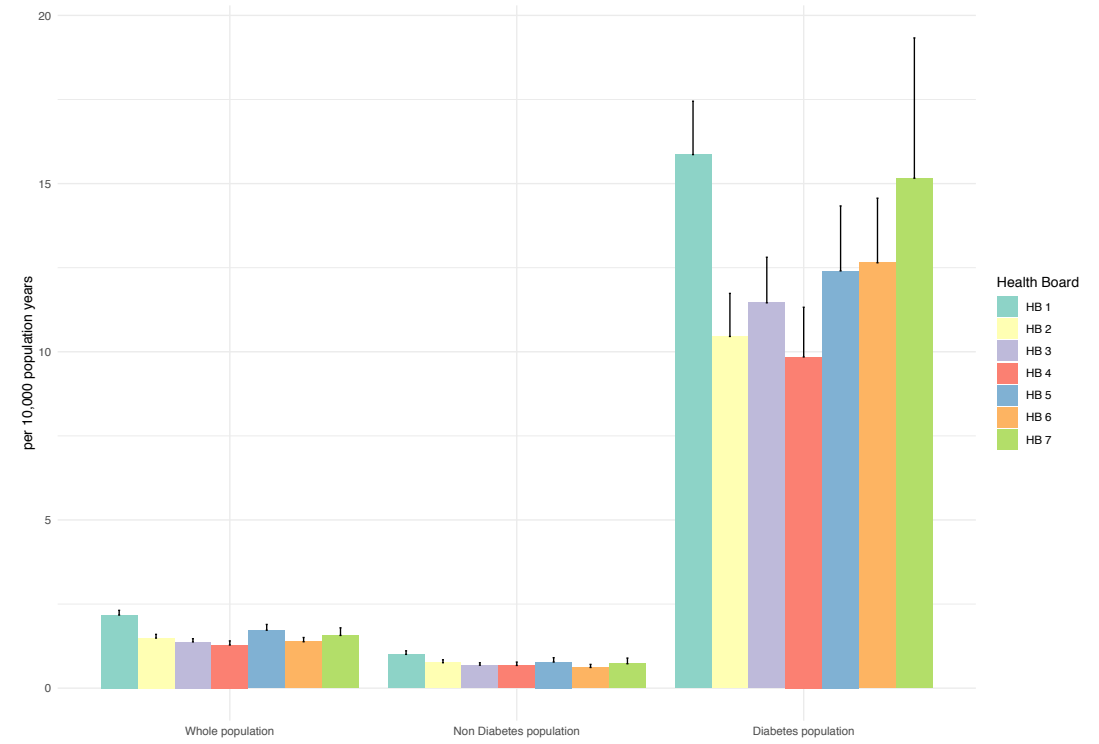


Figure 6.5 Incident Minor Amputation rate per 10 000 PY whole, non-diabetes and diabetes population by Health Board between 2008-2018



6.4.3.2 Total amputation rate stratified by Health Board

The trends in rates of total amputation over the whole period were similar to those seen for incident amputation between HBs. Again, the age standardised total any, major and minor amputation rate was highest for the whole population in HB1 at 5.7 [5.5-5.9], 2.4 [2.2-2.5] and 3.3 [3.2-3.5]/10 000 PY respectively (Figures 6.6-6.8). For any and major amputations the amputation rate was lowest in HB3, at 2.9 [2.8-3.1] and 1.0 [0.9-1.1]/10 000 PY giving a 2.0x and 2.4x variance between the highest and lowest rates for all and major amputations respectively. As was the case for incident amputation, the rate was lowest for major amputations in HB4 at 1.8 [1.7-2.0]/10 000 PY, 1.8x lower than the rate in HB1.

The age standardised rate for any, major and minor amputation in the non-diabetes population was highest in HB1 at 2.5 [2.3-2.7], 1.3 [1.2-1.4] and 1.2 [1.1-1.3]/10 000 PY respectively. The rate for any amputation was lowest in HB3, HB4 and HB7 at 1.5 [1.3-1.7]/10 000 PY, 1.7x lower than the highest rate. For major amputation the rate was lowest in HB3 at 0.6 [0.6-0.7]/10 000 PY, 2.2x lower than the highest rate. The rate for minor amputation was lowest in HB3, HB4, HB6 and HB7 at 0.8 [0.7-1.0]/10 000 PY, 1.5x lower than the highest rate.

In the population with diabetes the total any, major and minor amputation rate was again highest in HB1 at 41.2 [38.8-43.7], 13.9 [12.5-15.3] and 27.3 [25.3-29.4]/10 000 PY respectively. The variance in the rates between the HBS was greater than for incident amputation. HB4 had the lowest rates of any amputation at 23.7 [21.7-25.9]/10 000 PY, giving a 1.7x variance in rates. HB3 had the lowest major amputation rate at 5.6 [4.7-6.5]/10 000 PY, a 2.5x variance. The minor amputation rate was lowest in HB2 with 16.0 [14.5-17.5]/10 000 PY, 1.7x lower than the rate in HB1.

Figure 6.6 Total Any Amputation rate per 10 000 PY whole, non-diabetes and diabetes population by Health Board between 2008-2018

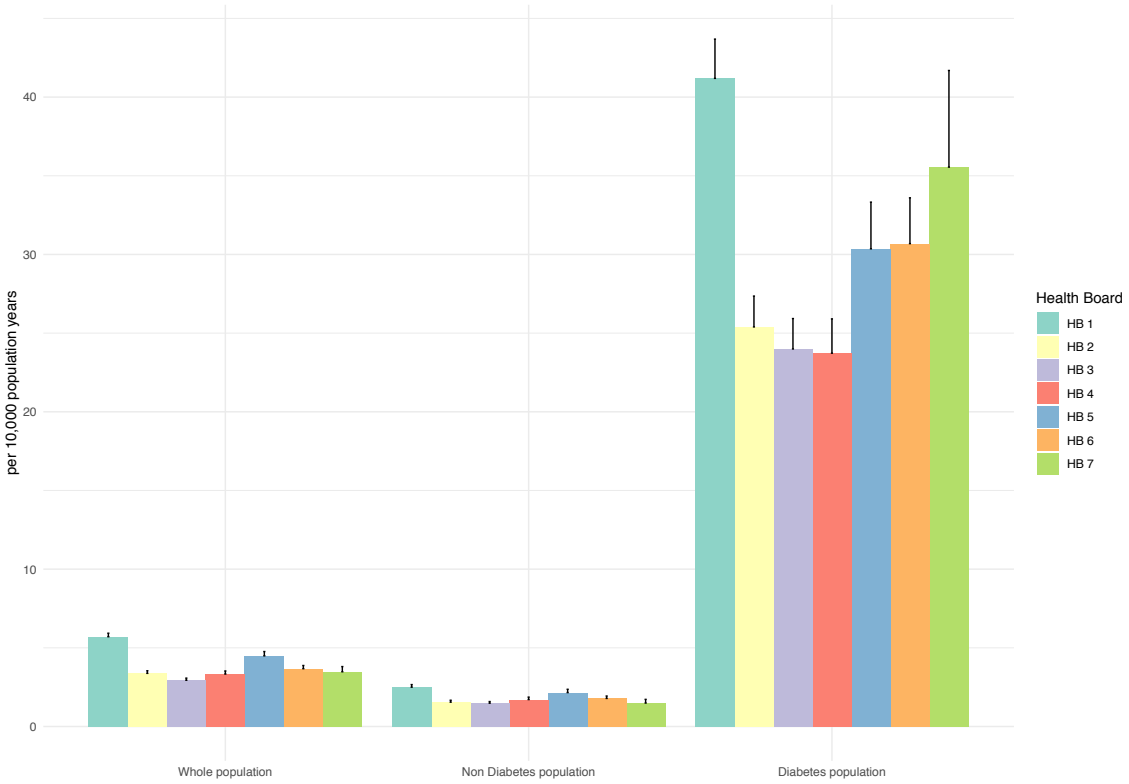


Figure 6.7 Total Major Amputation rate per 10 000 PY whole, non-diabetes and diabetes population by Health Board between 2008-2018

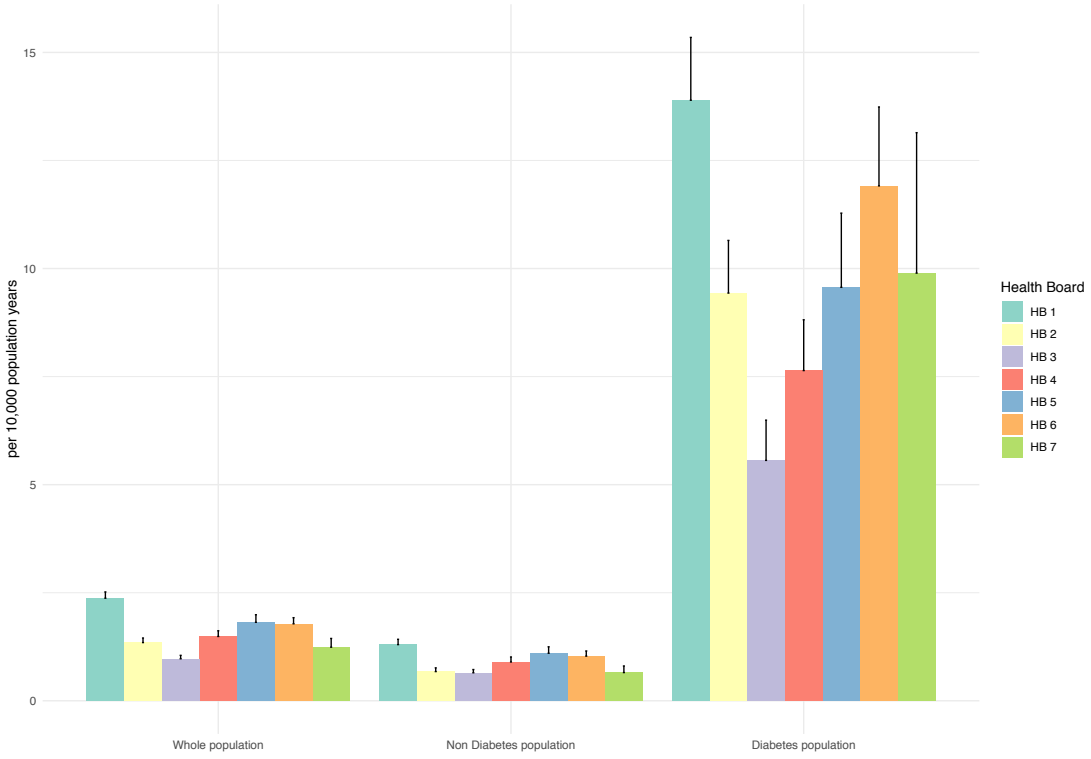
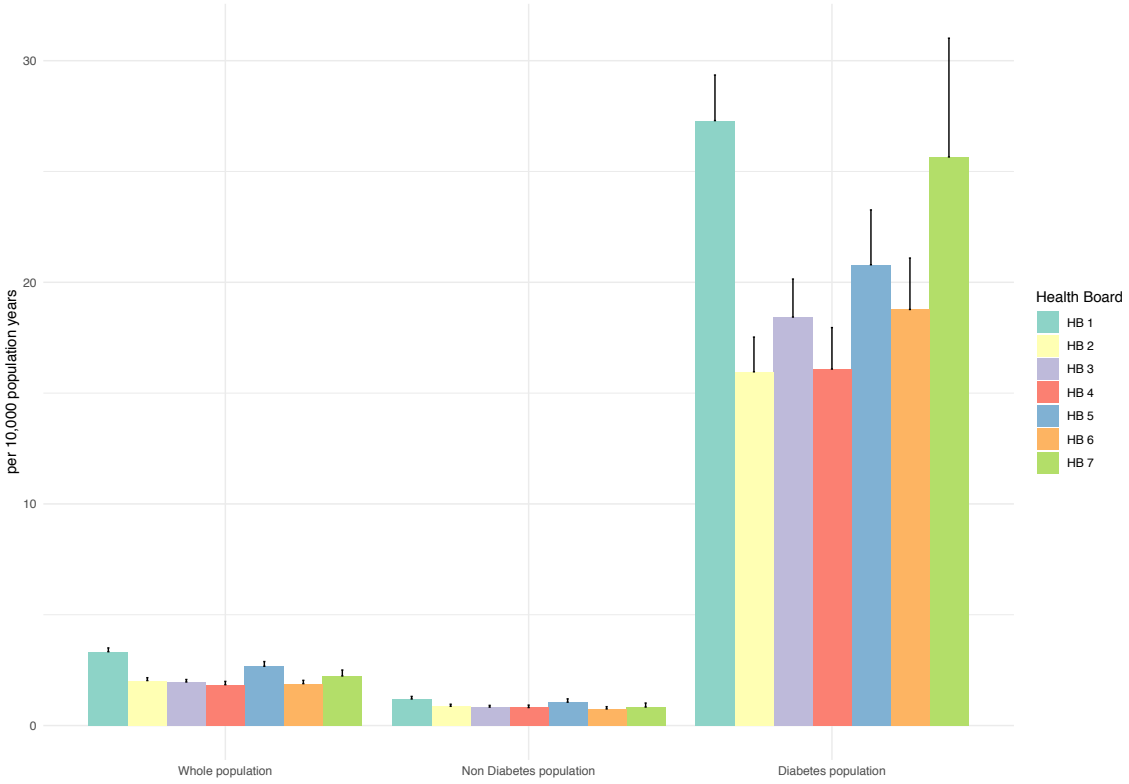


Figure 6.8 Total Minor Amputation rate per 10 000 PY whole, non-diabetes and diabetes population by Health Board between 2008-2018



6.4.3.3 Change in incident amputation rate over time stratified by Health Board

When looking at the population as a whole, there was no statistically significant change in rate of any incident amputation type in any population when comparing the start of the time period, 2008-2013, to the end of the time period, 2013-2018, except for the rate of minor amputations in the total population. This rate increased 1.1-fold [1.04-1.16] from 1.5 [1.4-1.6] to 1.6 [1.6-1.7]/ 10 000 PY. When stratified into the two time periods the trends within the HBs were similar to that seen in the in the whole period analysis. The change in the age-sex standardised incident amputation rates for each HB are displayed in Table 6.6 and Figures 6.9-6.11. There was no significant change in the rate of any incident amputation type for HB4 and 5, for any population, between the two periods.

There was a statistically significant increase in the rate of major amputation in the non-diabetic population in HB7 increasing 1.7-fold [1.23-2.22] from 0.4 [0.2-0.5] to 0.7 [0.5-0.9] amputations /10 000 PY. A decrease in incident major amputation rate was more commonly seen with HB2 and HB3 both decreasing their whole population major amputation rate 0.8-fold from 1.3 [1.1-1.4] to 1.0 [0.9-1.1] and 0.9 [0.8-1.0] to 0.7 [0.6-0.8]/10 000 PY respectively. This was driven by a reduction in rates in the diabetes population in HB2, a 0.7 fold reduction (9.0[7.5-10.7] - 6.2[5.1-7.6]/10 000 PY) and by a reduction in rate in the non-diabetes population in HB3: a 0.8 fold reduction (0.6[0.5-0.7]-0.5[0.4-0.6]/10 000 PY).

The incidence of incident minor amputations in the total population significantly increased in HB6 from 1.2 [1.1-1.4] to 1.5 [1.3-1.7] amputations per 10 000 PY. There was a significant increase in the rate of minor amputations performed in the population with diabetes in HB1, increasing 1.2-fold from 14.2 [12.3-16.3] to 17.2 [15.1-19.4] amputations /10 000 PY. There was no significant reduction in minor amputation rates seen in any HB.

Table 6.6 Incident Amputation rate per 10 000 PY and direct standardised rate ratio between the time periods 2008-2013 and 2013-2018, relative risk of amputation associated with diabetes and major minor amputation ratio in the population with and without diabetes stratified by Health Board

	Any			Major			Minor			Major-Minor ratio	
	2008-2013	**2013-2018**	***DSR ratio***	**2008-2013**	**2013-2018**	***DSR ratio***	**2008-2013**	**2013-2018**	***DSR ratio***	**2008-2013**	**2013-2018**
Health Board 1 [95% CI]											
ARt	3.4	3.6	*1.0*	1.9	1.9	*1.1*	2.0	2.3	*1.1*	1.1	**1.17**
	[3.19-3.66]	[3.34-3.81]	*[0.95-1.14]*	[1.68-2.03]	[1.77-2.11]	*[0.92-1.18]*	[1.86-2.23]	[2.08-2.45]	*[0.99-1.23]*	[0.98-1.23]	**[1.05-1.29]**
ARn	2.0	2.0	*1.0*	1.1	1.1	*1.1*	1.0	1.0	*1.0*	0.94	0.88
	[1.77-2.16]	[1.77-2.16]	*[0.86-1.14]*	[0.92-1.21]	[0.97-1.26]	*[0.86-1.23]*	[0.86-1.15]	[0.84-1.12]	*[0.78-1.17]*	[0.75-1.14]	[0.69-1.07]
ARd	20.0	22.3	*1.1*	10.3	11.6	*1.1*	14.2	17.2	***1.2***	**1.38**	**1.48**
	[17.72-22.4]	[19.99-24.8]	*[0.96-1.28]*	[8.68-11.98]	[9.94-13.47]	*[0.92-1.35]*	[12.3-16.26]	[15.11-19.4]	***[1.03-1.4]***	**[1.17-1.59]**	**[1.28-1.67]**
Relative risk	**10.2**	**11.4**		**9.7**	**10.5**		**14.2**	**17.6**			
	[10.02-10.3]	**[11.24-11.5]**		**[9.45-9.86]**	**[10.28-10.7]**		**[13.95-14.3]**	**[17.4-17.74]**			
Health Board 2 [95% CI]											
ARt	2.4	2.3	*1.0*	1.3	1.0	***0.8***	1.4	1.6	*1.1*	1.12	**1.6**
	[2.21-2.58]	[2.12-2.48]	*[0.85-1.07]*	[1.12-1.4]	[0.87-1.1]	***[0.62-0.94]***	[1.26-1.55]	[1.43-1.73]	*[0.99-1.26]*	[0.97-1.26]	**[1.45-1.75]**
ARn	1.4	1.2	*0.9*	0.7	0.5	*0.8*	0.8	0.8	*1.0*	1.15	**1.52**
	[1.22-1.53]	[1.09-1.37]	*[0.73-1.05]*	[0.55-0.76]	[0.41-0.6]	*[0.53-1.01]*	[0.64-0.87]	[0.65-0.88]	*[0.81-1.23]*	[0.93-1.37]	**[1.29-1.76]**
ARd	16.1	14.3	*0.9*	9.0	6.2	***0.7***	10.3	10.8	*1.1*	1.14	**1.74**
	[13.99-18.1]	[12.52-16.3]	*[0.71-1.08]*	[7.48-10.71]	[5.07-7.55]	***[0.43-0.95]***	[8.63-12.1]	[9.26-12.57]	*[0.83-1.28]*	[0.9-1.38]	**[1.49-1.98]**
Relative risk	**11.7**	**11.7**		**13.8**	**12.4**		13.7	14.1			
	[11.51-11.9]	**[11.51-11.9]**		**[13.54-14.0]**	**[12.14-12.7]**		[13.46-13.9]	[13.9-14.34]			
Health Board 3 [95% CI]											
ARt	2.1	2.0	*0.9*	0.9	0.7	***0.8***	1.4	1.4	*1.0*	**1.48**	**2.01**
	[1.96-2.27]	[1.82-2.12]	*[0.83-1.04]*	[0.82-1.03]	[0.62-0.8]	***[0.61-0.93]***	[1.25-1.5]	[1.3-1.55]	*[0.92-1.17]*	**[1.34-1.63]**	**[1.86-2.16]**
ARn	1.3	1.1	*0.9*	0.6	0.5	***0.8***	0.7	0.7	*1.0*	1.14	**1.44**
	[1.15-1.4]	[0.97-1.21]	*[0.71-1]*	[0.54-0.73]	[0.4-0.56]	***[0.54-0.96]***	[0.63-0.82]	[0.59-0.78]	*[0.76-1.13]*	[0.94-1.33]	**[1.23-1.64]**
ARd	14.4	14.3	*1.0*	5.0	3.9	*0.8*	10.9	12.1	*1.1*	**2.18**	**3.07**
	[12.46-16.5]	[12.48-16.4]	*[0.8-1.19]*	[3.9-6.23]	[3-5]	*[0.45-1.12]*	[9.17-12.71]	[10.4-13.92]	*[0.89-1.33]*	**[1.9-2.46]**	**[2.78-3.36]**
Relative risk	**11.3**	**13.1**		**7.8**	**8.2**		**15.0**	**17.6**			
	[11.12-11.5]	**[12.97-13.3]**		**[7.57-8.11]**	**[7.94-8.53]**		**[14.8-15.21]**	**[17.42-17.8]**			
Health Board 4 [95% CI]											
ARt	2.3	2.0	*0.9*	1.2	1.2	*1.0*	1.4	1.2	*0.9*	1.13	1.05
	[2.09-2.53]	[1.81-2.2]	*[0.74-1.0]*	[1.05-1.37]	[1-1.3]	*[0.77-1.14]*	[1.2-1.54]	[1.05-1.36]	*[0.71-1.06]*	[0.95-1.31]	[0.87-1.23]
ARn	1.4	1.2	*0.9*	0.7	0.6	*0.9*	0.8	0.6	*0.8*	1.09	0.96
	[1.18-1.55]	[1.03-1.37]	*[0.69-1.07]*	[0.57-0.83]	[0.52-0.77]	*[0.66-1.19]*	[0.62-0.9]	[0.5-0.74]	*[0.55-1.08]*	[0.83-1.35]	[0.69-1.23]
ARd	16.4	12.8	*0.8*	8.3	7.4	*0.9*	11.1	8.3	*0.8*	**1.34**	1.12
	[13.99-19.1]	[10.8-14.98]	*[0.55-1.0]*	[6.62-10.24]	[5.94-9.16]	*[0.6-1.2]*	[9.1-13.39]	[6.74-10.08]	*[0.48-1.02]*	**[1.05-1.62]**	[0.83-1.4]
Relative risk	**12.1**	**10.7**		**11.9**	**11.5**		**14.7**	**13.5**			
	[11.89-12.3]	**[10.47-10.9]**		**[11.65-12.2]**	**[11.25-11.8]**		**[14.42-14.9]**	**[13.18-13.7]**			

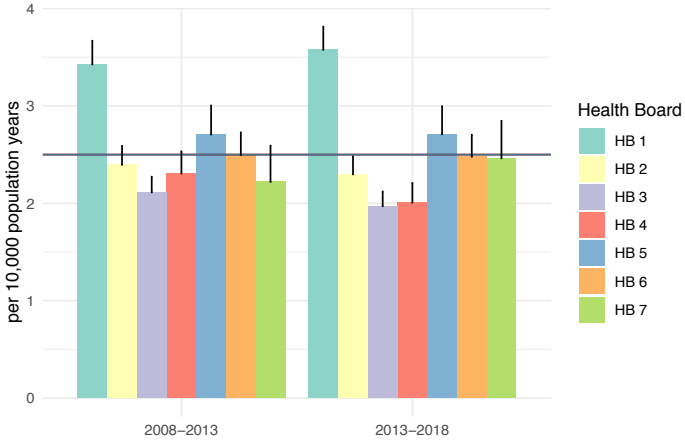
Health Board 5 [95% CI]											
ARt	2.7	2.7	*1.0*	1.5	1.4	*1.0*	1.6	1.8	*1.1*	1.11	**1.26**
	[2.43-3]	[2.44-2.99]	*[0.86-1.15]*	[1.25-1.67]	[1.24-1.64]	*[0.79-1.19]*	[1.39-1.83]	[1.58-2.03]	*[0.94-1.3]*	[0.91-1.3]	**[1.07-1.44]**
ARn	1.6	1.4	*0.9*	1.0	0.9	*0.9*	0.7	0.8	*1.1*	0.72	0.91
	[1.33-1.8]	[1.23-1.68]	*[0.72-1.14]*	[0.81-1.19]	[0.71-1.04]	*[0.61-1.14]*	[0.56-0.89]	[0.63-0.97]	*[0.81-1.41]*	[1.43-1.01]	[0.63-1.19]
ARd	16.3	16.1	*1.0*	6.7	7.1	*1.1*	11.8	13.0	*1.1*	**1.76**	**1.82**
	[13.5-19.4]	[13.46-19.1]	*[0.74-1.24]*	[4.98-8.81]	[5.38-9.12]	*[0.68-1.43]*	[9.5-14.51]	[10.6-15.65]	*[0.82-1.38]*	**[1.42-2.1]**	**[1.51-2.14]**
Relative risk	**10.5**	**11.2**		**6.7**	**8.2**		16.5	16.3			
	[10.24-10.7]	**[10.92-11.4]**		**[6.4-7.07]**	**[7.83-8.47]**		[16.2-16.79]	[16.1-16.61]			
Health Board 6 [95% CI]											
ARt	2.5	2.5	*1.0*	1.6	1.3	*0.8*	1.2	1.5	***1.2***	**0.78**	1.14
	[2.27-2.72]	[2.26-2.7]	*[0.87-1.12]*	[1.41-1.77]	[1.16-1.48]	*[0.67-1.0]*	[1.08-1.4]	[1.34-1.68]	***[1.05-1.39]***	**[0.61-0.95]**	[0.98-1.31]
ARd	1.4	1.3	*0.9*	0.9	0.8	*0.9*	0.6	0.6	*1.1*	**0.65**	0.8
	[1.24-1.61]	[1.17-1.51]	*[0.76-1.12]*	[0.76-1.05]	[0.67-0.93]	*[0.65-1.11]*	[0.48-0.71]	[0.52-0.76]	*[0.81-1.35]*	**[0.4-0.9]**	[0.56-1.05]
ARn	17.3	18.3	*1.1*	10.6	8.8	*0.8*	11.2	13.8	*1.2*	1.06	**1.58**
	[14.56-20.4]	[15.52-21.4]	*[0.83-1.29]*	[8.41-12.96]	[6.84-10.91]	*[0.52-1.14]*	[8.95-13.74]	[11.4-16.53]	*[0.96-1.51]*	[0.76-1.36]	**[1.29-1.87]**
Relative risk	**12.2**	**13.7**		**11.7**	**11.0**		**18.9**	**21.6**			
	[11.98-12.4]	**[13.51-13.9]**		**[11.38-11.9]**	**[10.69-11.3]**		**[18.61-19.2]**	**[21.3-21.85]**			
Health Board 7 [95% CI]											
ARt	2.2	2.5	*1.1*	1.0	1.0	*1.1*	1.4	1.7	*1.2*	**1.47**	**1.66**
	[1.88-2.59]	[2.11-2.84]	*[0.9-1.32]*	[0.76-1.24]	[0.82-1.3]	*[0.74-1.38]*	[1.17-1.74]	[1.44-2.05]	*[0.94-1.46]*	**[1.16-1.77]**	**[1.38-1.94]**
ARn	1.0	1.3	*1.2*	0.4	0.7	***1.7***	0.7	0.7	*1.1*	**1.77**	1.13
	[0.79-1.3]	[1.01-1.57]	*[0.92-1.56]*	[0.24-0.53]	[0.47-0.86]	***[1.23-2.22]***	[0.48-0.9]	[0.55-0.98]	*[0.7-1.51]*	**[1.28-2.26]**	[0.73-1.54]
ARd	21.9	22.0	*1.0*	10.1	7.2	*0.7*	13.6	17.6	*1.3*	1.35	**2.46**
	[16.1-28.67]	[16.12-28.8]	*[0.61-1.4]*	[6.3-14.73]	[4.03-11.2]	*[0.09-1.34]*	[9.1-18.97]	[12.4-23.83]	*[0.83-1.77]*	[0.81-1.88]	**[1.89-3.03]**
Relative risk	**21.3**	**17.3**		**26.4**	**10.9**		**20.1**	**23.6**			
[95% CI]	**[20.96-21.7]**	**[16.98-17.7]**		**[25.79-26.9]**	**[10.31-11.4]**		**[19.64-20.6]**	**[23.2-24.03]**			

Age and gender rates standardised to Welsh population ONS midyear estimate 2013. Statistically significant rates in bold.

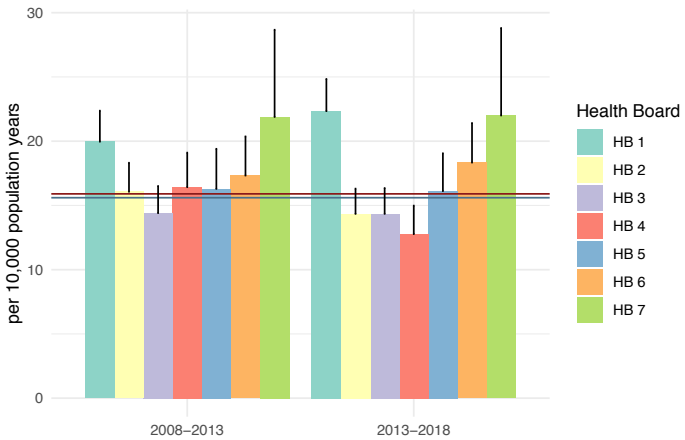
ARt- Amputation rate total population, ARd - Amputation rate diabetic population, ARn - Amputation rate non diabetic population, RR- relative risk of amputation, diabetic population compared to non-diabetic population.

Figure 6.9 Rate of incident any amputation in the time periods 2008-2013 and 2013-2018 in each Health Board, stratified by population

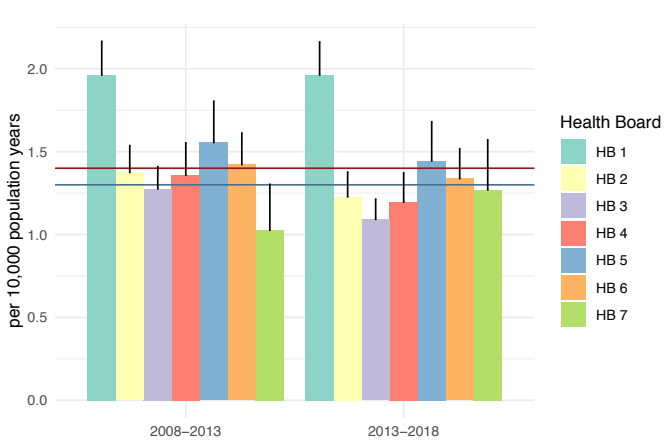
A-Total Population



B-Diabetes Population



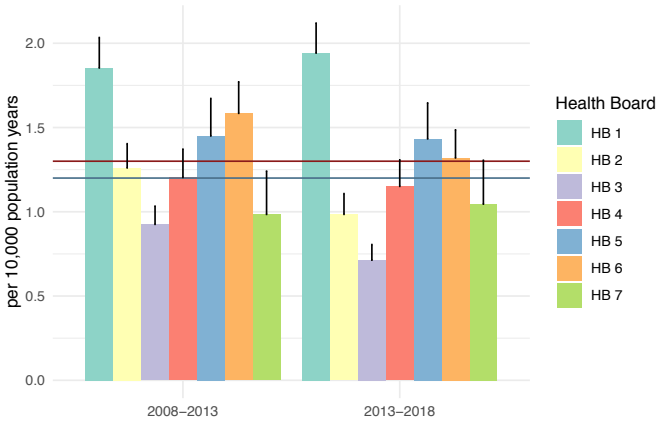
C-Non-Diabetes Population



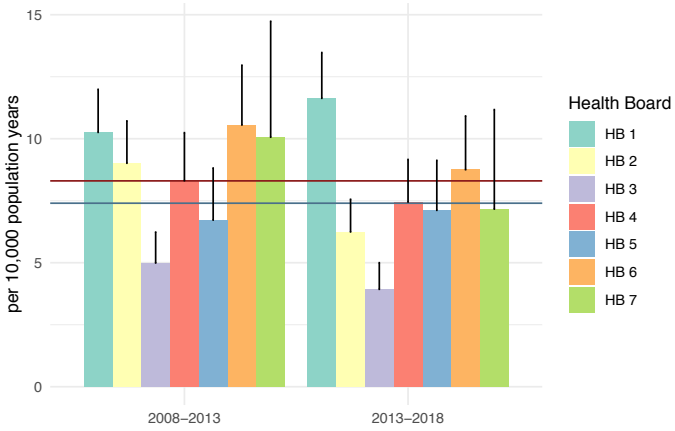
red line 2008-2013 all Wales all incidence rate. Blue line 2013-2018 all Wales incidence rate.

Figure 6.10 Rate of incident major amputation in the time periods 2008-2013 and 2013-2018 in each Health Board, stratified by population

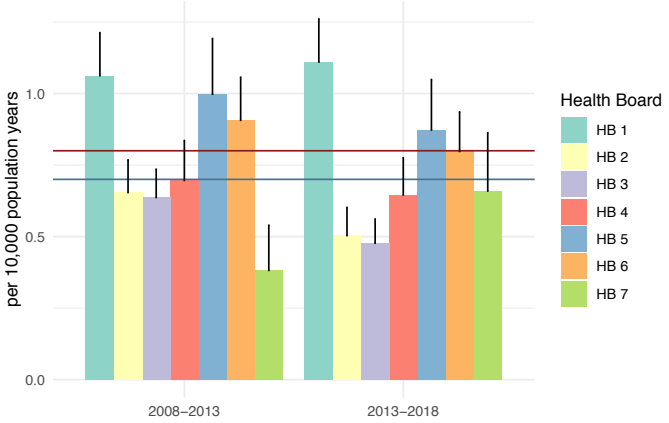
A-Total Population



B-Diabetes Population



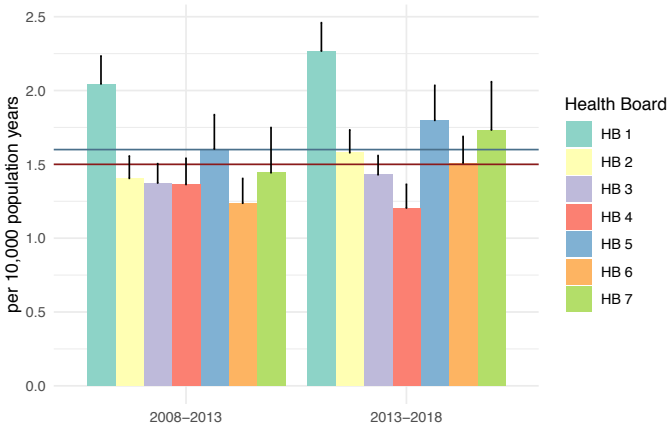
C-Non-Diabetes Population



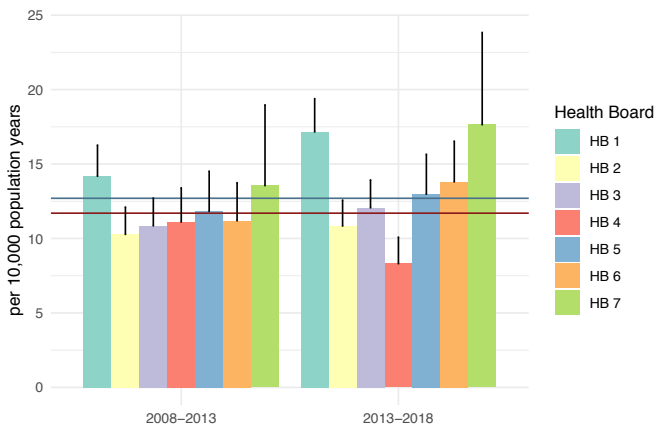
red line 2008-2013 all Wales all incidence rate. Blue line 2013-2018 all Wales incidence rate.

Figure 6.11 Rate of incident minor amputation in the time periods 2008-2013 and 2013-2018 in each Health Board, stratified by population

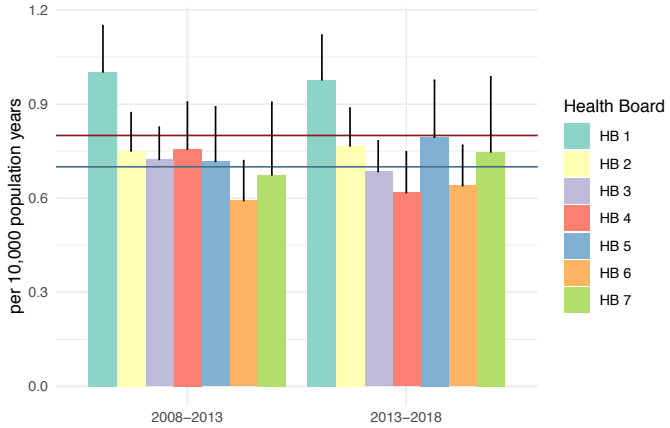
A- Total population



B- Diabetes population



C-Non-Diabetes Population



red line 2008-2013 all Wales all incidence rate. Blue line 2013-2018 all Wales incidence rate.

6.4.3.4 Relative risk of incident amputation caused by diabetes in each Health Board

For the whole observation period the age-sex standardised amputation rate for incident any amputation was greater in the diabetes population in all HBs. It was greatest in HB7 with those in the diabetes population having 21.3-fold [20.96-21.7] increased risk of amputation compared to the non-diabetes population between 2008-2013. When comparing the first and last six-year periods of observation, the relative risk within HB7 decreased significantly to a relative risk of 17.3 [16.98-17.2]. This change was driven by an increased rate of incident amputation in the non-diabetes population and there was no significant decline in the rate of incident amputation in the diabetes population. HB4 also saw a reduction in relative risk between the two periods, but this was due to a decline in the rate of incident any amputation in the population with diabetes. There was an increase in the relative risk of incident any amputation associated with diabetes of in HB 1 and HB6 driven by an increase in rates of amputations in the population with diabetes. An increase in the relative risk between the two periods was also seen in HB3, driven by a greater decline in the rate of any amputation in the non-diabetes population than in the diabetes population.

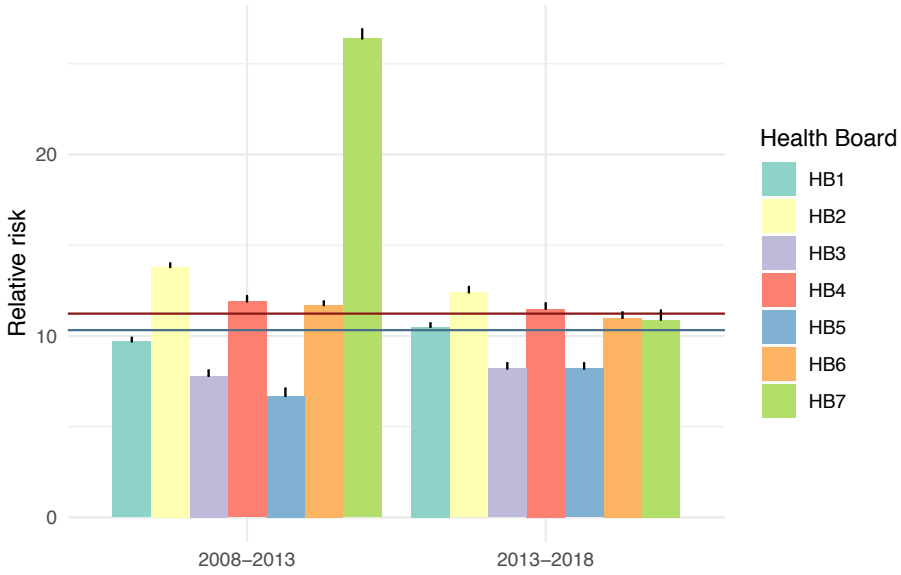
For major amputation the trend was similar with the relative risk of major incident amputation associated with diabetes above 1 for all HBs. The greatest relative risk was seen in HB7 with those in the diabetes population 26.4 [25.79-26.9] fold more likely to undergo a major amputation than those in the non-diabetes population (Figure 6.12A). There was a greater decline in this rate than that seen for any amputation, with a reduction in the relative risk associated with diabetes to 10.9 [10.31-11.4] due to an increase in the rate of major amputation in the non-diabetes population and a reduction in rate in the diabetes population. Again, there was an increase in relative risk in HB1 and HB 6 due to an increase in the major amputation rate in the diabetes population. No other HB saw a significant change in relative risk between the periods.

As in the whole population analysis, the relative risk of incident amputation associated with diabetes was greatest for minor amputation in all HBs (Figure 6.12 b). HB1, HB3, HB6 and HB7 all saw a significant increase in the relative risk of minor amputation b associated with diabetes between the two periods, all due to an increase in the rate of minor amputations performed in the diabetes population. HB4 saw a significant reduction in relative risk (14.7

[14.42-14.9]-13.5 [13.18-13.7]) due to a greater reduction in the rate of minor amputations performed in patients with diabetes.

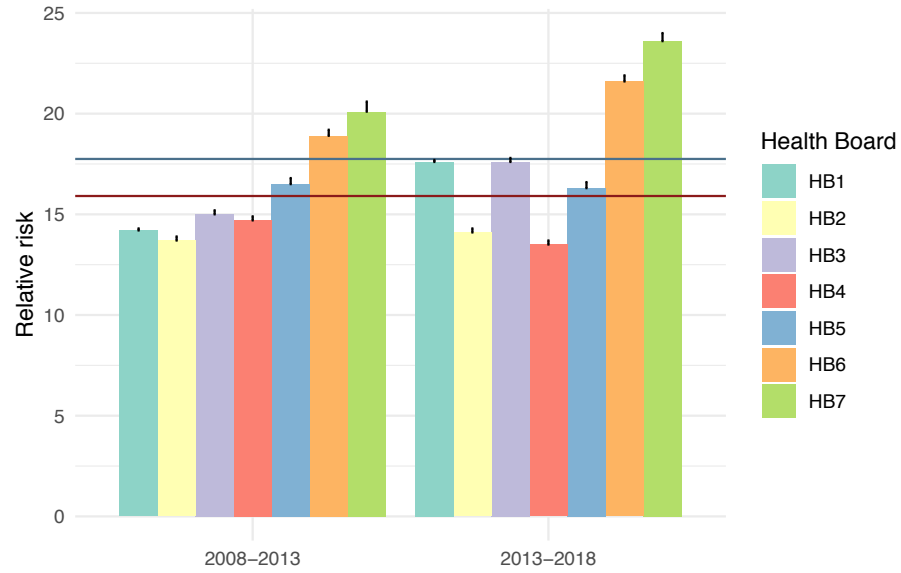
Figure 6.12 Relative risk of incident amputation in diabetes population vs non diabetes population (A) major amputation (B) minor amputation

A- Realtive risk of major amputation



red line 2008-2013 all Wales all incidence rate. Blue line 2013-2018 all Wales incidence rate.

B-Realtive risk of minor amputation



red line 2008-2013 all Wales all incidence rate. Blue line 2013-2018 all Wales incidence rate.

6.4.3.5 Incident Major-Minor ratio stratified by Health Board

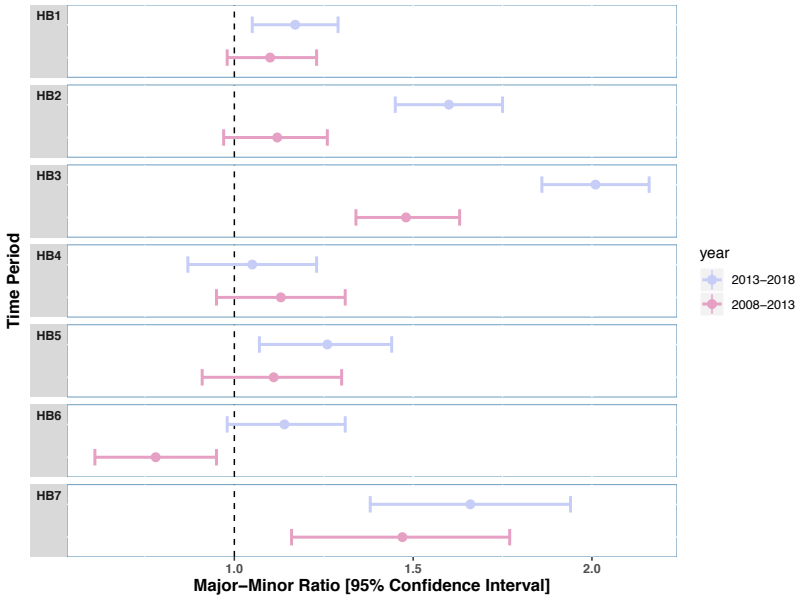
In the 2008-2013 period there was a significantly greater number of minor amputations performed in the whole population in HB3 and HB7 and significantly fewer in HB6 (Figure 6.13). In 2013-2018 the number of HBs with a positive major- minor ratio increased with HB2, HB3, HB4 and HB7 having significantly higher rates of minor amputation in the whole population. Within this period no HB had rates of minor amputation lower than that of major amputation.

In the population with diabetes within the 2008-2013 period there was an excess of minor amputations in the diabetes population with a major to minor ratio higher than the non-diabetes population in HB1, HB3, HB4 and HB5. Again, the number of HBs with a positive major-minor ratio increased in the 2013-2018 period with all HBs except HB4 showing an excess of minor amputations. HB3 had the highest major minor ratio in both periods (08-13: 2.18 [1.9-2.46]; 13-18: 3.07 [2.78-3.36]) and the lowest major amputation rate of the HBs for patients with diabetes.

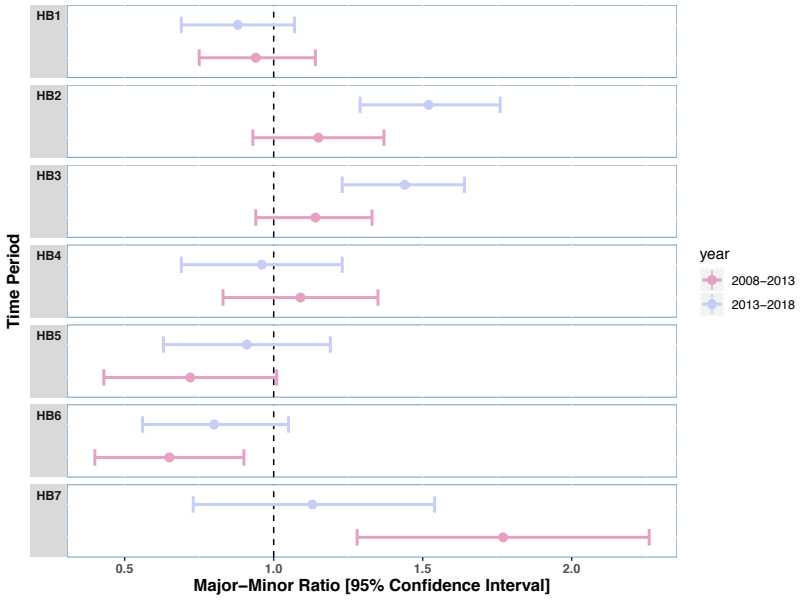
With respect to the non-diabetes population, the major-minor ratios were generally smaller. The major-minor amputation ratio for incident amputations was the highest in HB7 in the first period at 1.77 [1.28-2.26] then decreased significantly in the second period to 1.13 [0.73-1.54]. Significantly more major amputations were performed on people in the non-diabetes population in HB6 in the first period. This ratio increased significantly and there was no significant difference between rates of major and minor amputation for the 2013-2018 period. For the 2013-2018 period HB 2 and 3 had an excess in the rates of major amputation; all other HBs had no significant variance between major and minor amputation rates.

Figure 6.13 Major-Minor ratio for incident amputation in 2008-2013 and 2013-2018 period stratified by Health Board

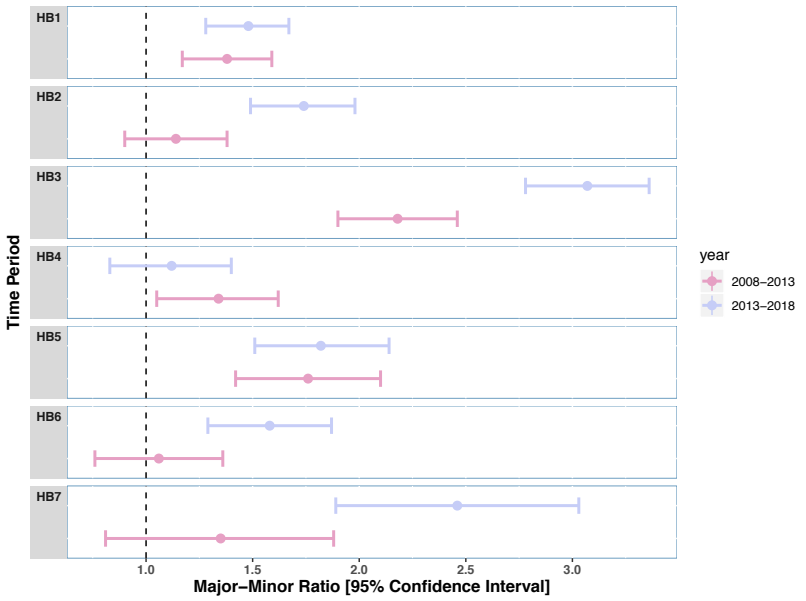
A-Total population



B - Non-diabetes Population



c- Diabetes Population



6.4.3.6 Change in Total Amputation rate over time stratified by Health Board

In the population as a whole, there was a 0.9-fold reduction in the total any amputation in the whole population (3.7 [3.5-3.8] to 3.5 [3.4-3.6]/10 000 PY) and a 1.2-fold increase in total minor amputations (2.1[2.0-2.1] to 2.4[2.4-2.5]/10 000 PY) between the periods 2008-2013 and 2013-2018. There was no significant change in rates for total any amputation in the non-diabetes population, but an increase in rate was seen in the population with diabetes. The rate of total any amputation in the diabetes population increased 1.1-fold (28.6[27.3-29.9] to 30.7[29.5-32.0]/10 000 PY) and this was driven by a 1.23-fold increase in minor amputations (18.1 [17.1-19.1] to 21.3 [20.3-22.3]/10 000 PY). The change in the age-sex standardised total amputation rates for each HB are displayed in Table 6.10 and Figures 6.14-6.16. Unlike for incident amputation, there was a significant change in amputation rates in all HBs in at least one population.

For total any amputation, there was a statistically significant increase seen in the rate in the whole and diabetes populations of HB1 increasing 1.2-fold (5.1 [4.84-5.41] to 6.2 [5.93-6.54]/10 000 PY) and 1.4-fold (34.4 [31.42-37.6] to 46.6 [43.18-50.1]/10 000 PY) respectively. An increase was also seen in HB7 in the whole population (3.1 [2.73-3.56] to 3.9 [3.42-4.33] amputations/10 000 PY) but this change was driven by an increase in the rates within the non-diabetes population with a 1.4-fold increase (1.2 [0.94-1.49] to 1.7 [1.38-2.02]/10 000 PY). The only HB that displayed a significant decrease in the rate of total any amputations in the diabetes population was HB4, with a 0.8-fold decrease in rates (28.6 [25.32-32.1] to 23.5 [20.8-26.42]/10 000 PY).

There was a statistically significant increase in the rate of major amputation in the diabetes population in HB1 increasing 1.2-fold from 12.3 [10.6-14.22] to 15.2 [13.27-17.2]/10 000 py and HB7 saw a 1.7-fold increase major amputation rate in the non- diabetes population (0.5 [0.31-0.63] to 0.8 [0.58-0.99]/10 000 PY). A decrease in major amputation rate was more commonly seen, HB 2 and HB3 both had a decrease in their whole population major amputation rate 0.8-fold from 1.5 [1.33-1.63] to 1.2 [1.07-1.33] and 1.1 [0.98-1.2] to 0.8 [0.74-0.94]/10 000 PY respectively. HB2 saw a reduction in the rate in both the diabetes and non-diabetes population and HB3 a 0.8-fold reduction in its non-diabetes population major amputation rate.

The incidence of minor amputations in the total population significantly increased in all HBs excluding HB4 with a maximum increase seen in HB6 and HB7 with a 1.4-fold increase in amputation rate (HB6: 1.6 [1.41-1.77] to 2.2 [1.95-2.36]; HB7: 1.9 [1.62-2.27] to 2.6 [2.25-3]). There was a significant increase in the rate of minor amputations performed in the population with diabetes in HB 1, 6 and 7, increasing 1.4-fold in HB1 and HB6 and 1.6-fold in HB7. There was no significant increase in the minor amputation rate in any HB for in the population without diabetes.

Table 6.7 Total Amputation rate per 10 000 PY and direct standardised rate ratio between the time periods 2008-2013 and 2013-2018, relative risk of amputation associated with diabetes and major minor amputation ratio in the population with and without diabetes stratified by Health Board

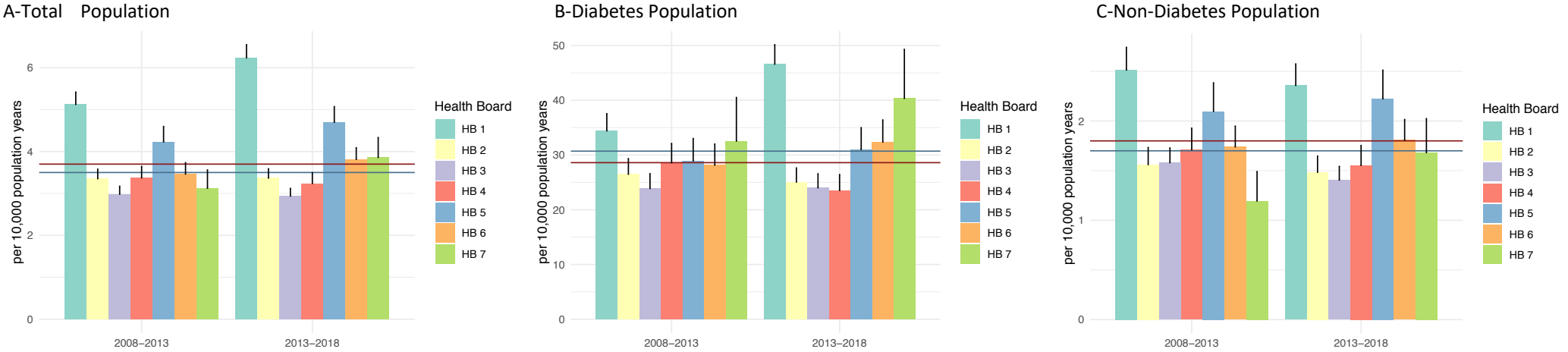
	Any		*DSR Ratio*	Major		*DSR Ratio*	Minor		*DSR ratio*	Major-Minor ratio	
	2008-2013	**2013-2018**		**2008-2013**	**2013-2018**		**2008-2013**	**2013-2018**		**2008-2013**	**2013-2018**
Health Board 1 [95% CI]											
ARt	5.1	6.2	***1.2***	2.3	2.5	*1.1*	2.9	3.7	***1.3***	**1.26**	**1.47**
	[4.84-5.41]	[5.93-6.54]	***[1.14-1.29]***	[2.07-2.46]	[2.33-2.72]	*[1-1.23]*	[2.65-3.08]	[3.48-3.95]	***[1.2-1.4]***	**[1.15-1.38]**	**[1.37-1.57]**
ARn	2.5	2.4	*0.9*	1.3	1.2	*0.9*	1.2	1.2	*0.98*	0.91	1
	[2.29-2.74]	[2.15-2.57]	*[0.81-1.06]*	[1.16-1.48]	[1.03-1.33]	*[0.72-1.07]*	[1.05-1.35]	[1.03-1.33]	*[0.81-1.16]*	[0.74-1.08]	[0.82-1.18]
ARd	34.4	46.6	***1.4***	12.3	15.2	***1.2***	22.1	31.4	***1.42***	**1.79**	**2.07**
	[31.42-37.6]	[43.18-50.1]	***[1.24-1.47]***	[10.6-14.22]	[13.27-17.2]	***[1.04-1.43]***	[19.7-24.64]	[28.6-34.34]	***[1.28-1.57]***	**[1.61-1.97]**	**[1.91-2.22]**
Relative risk	**13.7**	**19.8**		**9.4**	**12.9**		**18.4**	**26.6**			
	[13.6-13.81]	**[19.64-19.9]**		**[9.18-9.56]**	**[12.7-13.07]**		**[18.27-18.6]**	**[26.5-26.78]**			
Health Board 2 [95% CI]											
ARt	3.4	3.4	*1.0*	1.5	1.2	***0.8***	1.9	2.2	***1.2***	**1.27**	**1.8**
	[3.13-3.58]	[3.15-3.58]	*[0.91-1.1]*	[1.33-1.63]	[1.07-1.33]	***[0.67-0.96]***	[1.71-2.04]	[1.99-2.34]	***[1.04-1.27]***	**[1.13-1.4]**	**[1.66-1.93]**
ARn	1.6	1.5	*1.0*	0.7	0.6	***0.8***	0.8	0.9	*1.0*	1.18	**1.46**
	[1.4-1.73]	[1.33-1.64]	*[0.8-1.1]*	[0.61-0.83]	[0.5-0.7]	***[0.62-1.07]***	[0.72-0.97]	[0.76-1]	*[0.85-1.24]*	[0.97-1.39]	**[1.25-1.68]**
ARd	26.5	25.1	*1.0*	11.4	8.0	***0.7***	15.1	17.1	*1.1*	**1.32**	**2.14**
	[23.8-29.34]	[22.6-27.63]	*[0.8-1.09]*	[9.65-13.32]	[6.62-9.45]	***[0.46-0.93]***	[13.1-17.26]	[15.1-19.24]	*[0.95-1.31]*	**[1.12-1.53]**	**[1.93-2.36]**
Relative risk	**17.0**	**16.9**		**15.9**	**13.2**		**17.9**	**19.4**			
	[16.8-17.11]	**[16.7-17.03]**		**[15.69-16.1]**	**[12.98-13.5]**		**[17.66-18.1]**	**[19.2-19.57]**			
Health Board 3 [95% CI]											
ARt	3.0	2.9	*1.0*	1.1	0.8	***0.8***	1.9	2.1	***1.1***	**1.73**	**2.5**
	[2.8-3.17]	[2.76-3.12]	*[0.9-1.07]*	[0.98-1.2]	[0.74-0.94]	***[0.62-0.92]***	[1.74-2.04]	[1.95-2.25]	***[1.01-1.22]***	**[1.6-1.86]**	**[2.37-2.63]**
ARn	1.6	1.4	*0.9*	0.7	0.6	***0.8***	0.9	0.9	*1*	1.17	**1.54**
	[1.44-1.72]	[1.27-1.54]	*[0.76-1.02]*	[0.63-0.83]	[0.47-0.64]	***[0.56-0.96]***	[0.75-0.96]	[0.75-0.96]	*[0.83-1.17]*	[0.99-1.35]	**[1.35-1.73]**
ARd	23.9	24.0	*1.0*	6.4	4.8	*0.7*	17.5	19.3	*1.1*	**2.73**	**4.05**
	[21.3-26.6]	[21.6-26.57]	*[0.86-1.16]*	[5.16-7.81]	[3.72-5.91]	*[0.44-1.04]*	[15.27-19.8]	[17.1-21.57]	*[0.93-1.28]*	**[2.49-2.97]**	**[3.8-4.31]**
Relative risk	**15.1**	**17.1**		8.8	8.6		**20.5**	**22.6**			
	[14.97-15.3]	**[16.9-17.22]**		[8.56-9.05]	[8.32-8.86]		**[20.3-20.67]**	**[22.42-22.8]**			
Health Board 4 [95% CI]											
ARt	3.4	3.2	*1.0*	1.5	1.5	*1.0*	1.9	1.8	*0.9*	**1.28**	**1.2**
	[3.11-3.64]	[2.99-3.49]	*[0.85-1.07]*	[1.31-1.66]	[1.3-1.64]	*[0.83-1.16]*	[1.7-2.09]	[1.59-1.96]	*[0.79-1.08]*	**[1.12-1.44]**	**[1.05-1.36]**
ARn	1.7	1.6	*0.9*	0.8	0.8	*1.0*	0.9	0.7	*0.8*	1.08	0.92
	[1.51-1.92]	[1.36-1.75]	*[0.74-1.08]*	[0.68-0.97]	[0.67-0.95]	*[0.74-1.23]*	[0.74-1.05]	[0.62-0.88]	*[0.6-1.08]*	[0.84-1.32]	[0.68-1.16]
ARd	28.6	23.5	***0.8***	10.8	9.5	*0.9*	17.8	14.0	*0.8*	**1.65**	**1.48**
	[25.32-32.1]	[20.8-26.42]	***[0.66-0.99]***	[8.84-12.96]	[7.79-11.4]	*[0.62-1.14]*	[15.2-20.65]	[11.96-16.3]	*[0.57-1]*	**[1.41-1.89]**	**[1.24-1.72]**
Relative risk	**16.7**	**15.1**		**13.1**	**11.7**		**20.2**	**18.8**			
	[16.5-16.87]	**[14.97-15.3]**		**[12.88-13.4]**	**[11.5-11.99]**		**[19.95-20.4]**	**[18.61-19.1]**			

Health Board 5 [95% CI]											
ARt	4.2	4.7	*1.1*	1.9	1.8	*1.0*	2.4	2.9	***1.2***	**1.28**	**1.6**
	[3.88-4.59]	[4.34-5.07]	*[1-1.22]*	[1.63-2.1]	[1.59-2.04]	*[0.8-1.15]*	[2.11-2.65]	[2.61-3.18]	***[1.07-1.37]***	**[1.11-1.44]**	**[1.44-1.76]**
ARn	2.1	2.2	*1.1*	1.2	1.1	*0.9*	0.9	1.1	*1.2*	0.77	1.04
	[1.83-2.38]	[1.96-2.51]	*[0.88-1.24]*	[0.98-1.39]	[0.9-1.28]	*[0.68-1.16]*	[0.74-1.11]	[0.94-1.34]	*[0.98-1.5]*	[0.51-1.03]	[0.8-1.29]
ARd	28.9	31.0	*1.1*	9.4	9.3	*1.0*	19.5	21.6	*1.1*	**2.07**	**2.32**
	[25.19-33.0]	[27.3-34.99]	*[0.89-1.25]*	[7.33-11.85]	[7.33-11.63]	*[0.67-1.31]*	[16.45-22.9]	[18.55-25.0]	*[0.89-1.33]*	**[1.78-2.35]**	**[2.05-2.59]**
Relative risk	13.8	13.9		**7.97**	**8.6**		**21.33**	**19.1**			
	[13.6-13.98]	[13.76-14.1]		**[7.69-8.26]**	**[8.3-8.87]**		**[21.1-21.59]**	**[18.8-19.29]**			
Health Board 6 [95% CI]											
ARt	3.5	3.8	*1.1*	1.9	1.7	*0.9*	1.6	2.2	***1.4***	0.85	**1.3**
	[3.2-3.73]	[3.55-4.09]	*[1-1.2]*	[1.68-2.07]	[1.48-1.84]	*[0.74-1.03]*	[1.41-1.77]	[1.95-2.36]	***[1.21-1.5]***	[0.7-1]	**[1.16-1.44]**
ARn	1.7	1.8	*1.0*	1.1	1.0	*0.9*	0.7	0.8	*1.2*	**0.65**	0.83
	[1.54-1.94]	[1.61-2.01]	*[0.88-1.2]*	[0.9-1.21]	[0.84-1.13]	*[0.73-1.14]*	[0.56-0.82]	[0.69-0.96]	*[0.95-1.44]*	**[0.42-0.88]**	[0.61-1.05]
ARd	28.1	32.4	*1.2*	12.8	10.9	*0.9*	15.4	21.5	***1.4***	**1.2**	**1.97**
	[24.56-32]	[28.58-36.4]	*[0.97-1.33]*	[10.41-15.4]	[8.77-13.27]	*[0.57-1.13]*	[12.7-18.27]	[18.4-24.82]	***[1.17-1.63]***	**[0.94-1.46]**	**[1.72-2.22]**
Relative risk											
	16.2	**17.9**		12.1	11.1		**22.4**	**26.1**			
	[16.0-16.35]	**[17.74-18.1]**		[11.9-12.38]	[10.8-11.3]		**[22.1-22.63]**	**[25.9-26.35]**			
Health Board 7 [95% CI]											
ARt	3.1	3.9	***1.2***	1.2	1.2	*1.0*	1.9	2.6	***1.4***	**1.61**	**2.09**
	[2.73-3.56]	[3.42-4.33]	***[1.06-1.41]***	[0.95-1.47]	[1-1.52]	*[0.75-1.34]*	[1.62-2.27]	[2.25-3]	***[1.14-1.57]***	**[1.34-1.88]**	**[1.84-2.34]**
ARn	1.2	1.7	***1.4***	0.5	0.8	***1.7***	0.7	0.9	*1.23*	**1.6**	1.16
	[0.94-1.49]	[1.38-2.02]	***[1.12-1.7]***	[0.31-0.63]	[0.58-0.99]	***[1.24-2.14]***	[0.54-0.97]	[0.68-1.16]	*[0.85-1.61]*	**[1.14-2.05]**	[0.79-1.53]
ARd	32.5	40.3	*1.2*	12.9	8.7	*0.7*	19.6	31.7	***1.6***	**1.52**	**3.66**
	[25.5-40.5]	[32.3-49.3]	*[0.93-1.55]*	[8.54-18.18]	[5.21-12.95]	*[0.11-1.23]*	[14.2-25.95]	[24.5-39.79]	***[1.24-1.99]***	**[1.06-1.99]**	**[3.17-4.15]**
Relative risk	**27.2**	**24.0**		**28.0**	**11.1**		**26.8**	**35.1**			
	[26.9-27.56]	**[23.71-24.3]**		**[27.52-28.5]**	**[10.6-11.62]**		**[26.34-27.2]**	**[34.75-35.4]**			

Age and gender rates standardised to Welsh population ONS midyear estimate 2013. Statistically significant rates in bold.

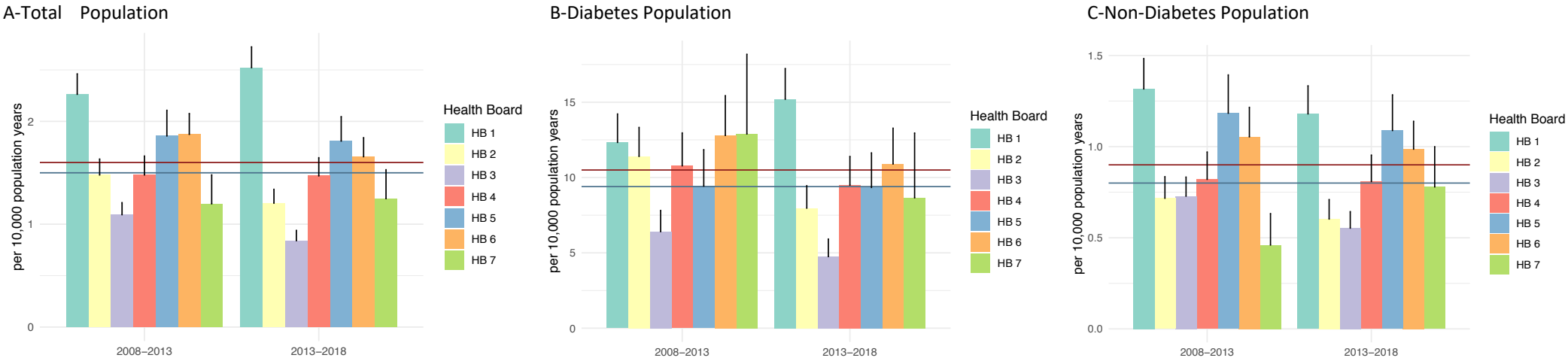
ARt- Amputation rate total population, ARd - Amputation rate diabetic population, ARn - Amputation rate non diabetic population, RR- relative risk of amputation, diabetic population compared to non-diabetic population.

Figure 6.14 Rate of total any amputation in the time periods 2008-2013 and 2013-2018 in each Health Board, stratified by population



red line 2008-2013 all Wales all incidence rate. Blue line 2013-2018 all Wales incidence rate.

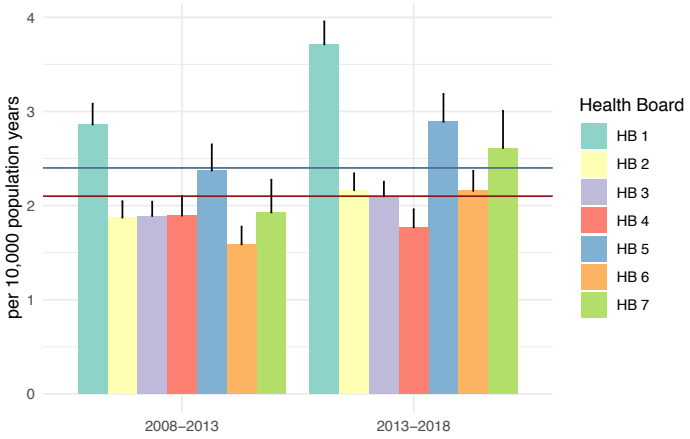
Figure 6.15 Rate of total major amputation in the time periods 2008-2013 and 2013-2018 in each Health Board, stratified by population



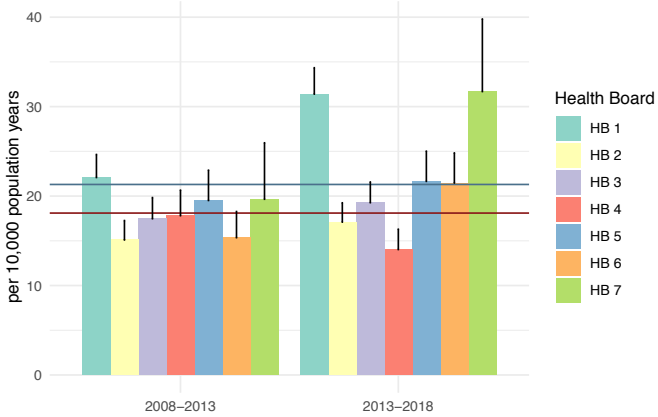
red line 2008-2013 all Wales all incidence rate. Blue line 2013-2018 all Wales incidence rate.

Figure 6.16 Rate of total minor amputation in the time periods 2008-2013 and 2013-2018 in each Health Board, stratified by population

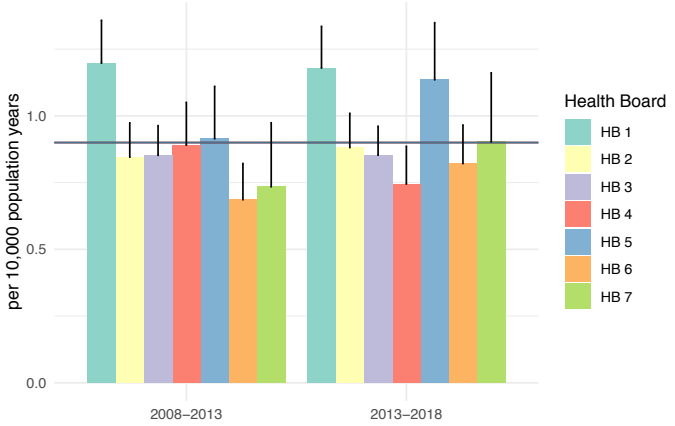
A-Total Population



B-Diabetes Population



C-Non-Diabetes Population



red line 2008-2013 all Wales all incidence rate. Blue line 2013-2018 all Wales incidence rate.

6.4.3.7 Relative risk of total amputation caused by diabetes stratified by Health Board

Over the whole observation period the age-sex standardised amputation rate for total any amputation was greater in the diabetes population in all HBs. As for incident amputation, the relative risk of any amputation associated with diabetes was greatest in HB7 with those in the diabetes population having 27.2-fold [26.9-27.56] increased risk of amputation compared to the non-diabetes population between 2008-2013. When comparing the first and last six-year periods of observation, the relative risk within HB7 decreased significantly. This change was driven by an increase in the rate of amputation in the non-diabetes population. HB4 also saw a reduction in the relative risk of amputation associated with diabetes between the two periods, but this was due to a decline in the rate of total any amputation in the population with diabetes greater than the decline in the non-diabetes population. There was an increase in the relative risk of total any amputation associated with diabetes in HB1 and HB6 driven by an increase in rates of amputation in the population with diabetes. An increase in the relative risk of total any amputation between the two periods was also seen in HB3 driven by a steeper decline in the rate of amputation in the non-diabetes population than in the diabetes population.

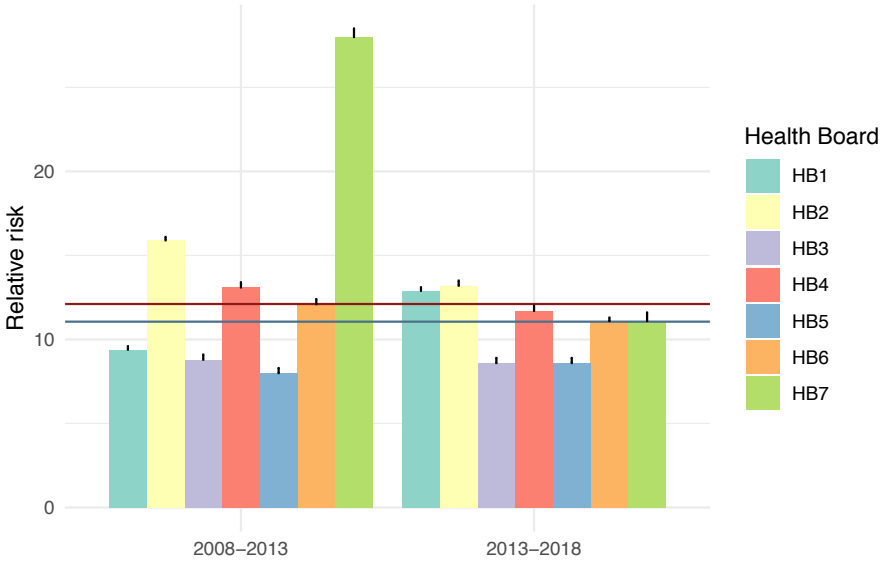
For total major amputation the trend was similar, with the relative risk of amputation associated with diabetes above 1 for all HBs. The greatest relative risk was seen in HB7 with those in the diabetes population 28.0-fold more likely to undergo a major amputation than those in the non-diabetes population (Figure 6.17a). There was a greater decline in this rate than that seen for total any amputation with a reduction in relative risk to 11.1 [10.6-11.62] due to an increase in the rate of major amputation in the non-diabetes population and a reduction in rate in the diabetes population. There was a reduction in relative risk between the two periods in HB2 and HB3 due to a greater reduction in the rate of amputations in the population with diabetes. Again, there was an increase in the relative risk of total major amputation associated with diabetes in HB1 due to an increase in amputation rate in the diabetes population and in HB5 due to an increase in rate in the diabetes population and a reduction in rate in the non-diabetes population.

The relative risk of total amputation in the diabetes population was greatest for minor amputation in all HBs (Figure 6.17b). There was a significant change in the relative risk

associated with diabetes between the two periods in all the HBs. HB1, HB2, HB3 and HB6 all saw a significant increase between the two periods with the greatest increase occurring in HB7 due to a greater increase in the minor amputation rate in the population with diabetes. HB 4 and HB5 both had a significant reduction in relative risk, HB4 due to a reduction in amputations in the population with diabetes and HB5 due to an increase in minor amputations in the non-diabetes population.

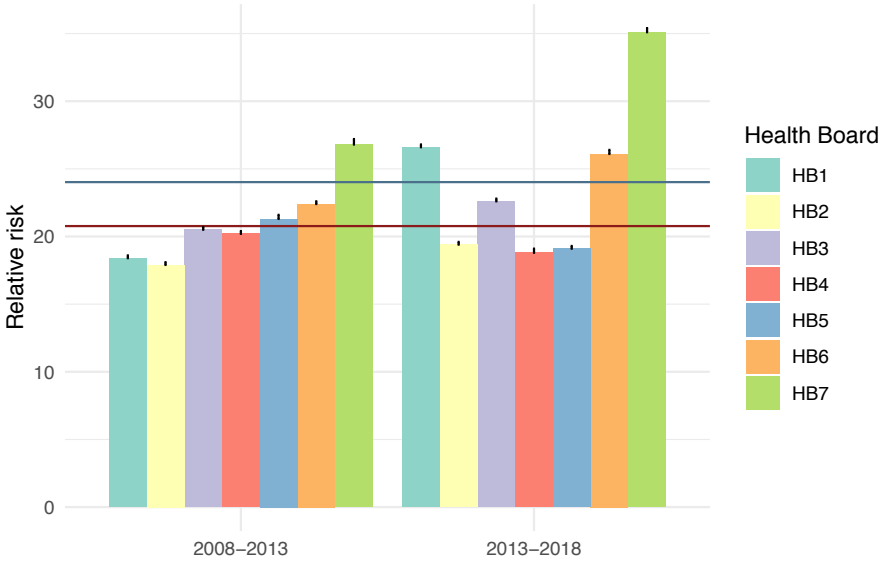
Figure 6.17 Relative risk of total amputation in diabetes population vs non diabetes population (A) major amputation (B) minor amputation

A- Realtive risk of major amputation



red line 2008-2013 all Wales all incidence rate. Blue line 2013-2018 all Wales incidence rate.

B- Realtive risk of minor amputation



red line 2008-2013 all Wales all incidence rate. Blue line 2013-2018 all Wales incidence rate.

6.4.3.8 Total Major-Minor ratio stratified by Health Board

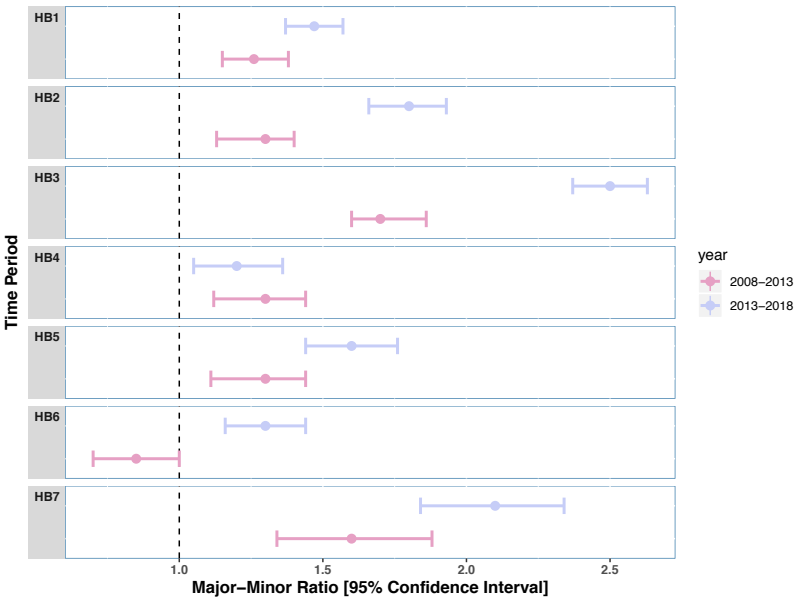
In the 2008-2013 period there was a significantly greater number of minor amputations in the whole population of all HBs apart from HB6 (Figure 6.18a). In the 2013-2018 period the ratio was above 1 for all HBs and had increased significantly in all HBs apart from HB4. Between the first and last time period no HB had a significant reduction in major-minor ratio.

In the first time period there was an excess of minor amputations in the diabetes population with a major-to-minor ratio higher than the non-diabetes population in all HBs (Figure 6.18b). This was maintained in the 2013-2018 period with the major-minor amputation rates increasing in all HBs apart from HB4 with a significant increase seen in HBs 2,3,6 and 7. As for incident amputation HB3 had the highest major-minor ratio in both periods (08/13: 2.73 [2.49-2.97]; 13/18: 4.05 [3.8-4.31]; and the lowest total major amputation rate of the HBs for patients with diabetes.

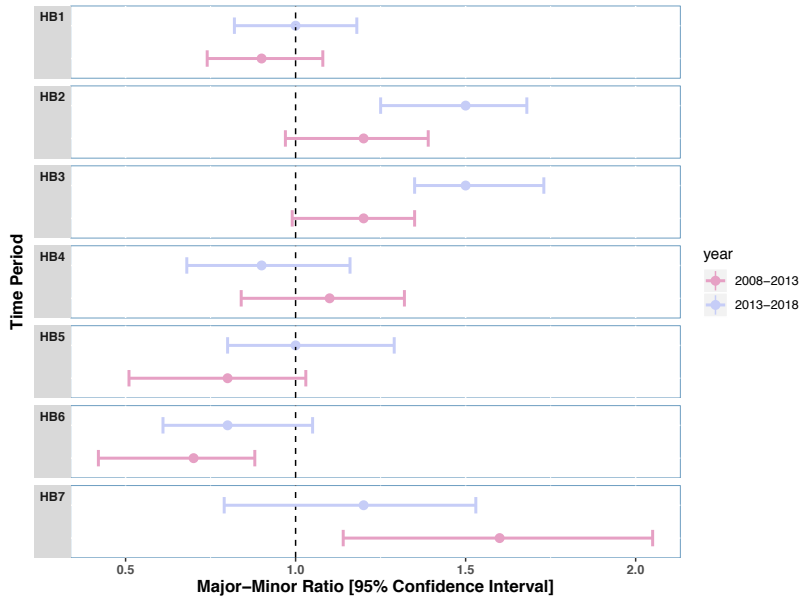
In the non-diabetes population the major-minor amputation ratio for total amputations in the first period was large in HB7 (1.6 [1.14-2.05]) then decreased significantly in the second period to 1.16 [0.79-1.53]. A greater number of major amputations were performed for patients in the non-diabetes population in HB6 in the first period. This ratio increased significantly with no significant difference between rates of major and minor amputation for the 2013-2018 period. For the 2013-2018 period HB 2 and 3 had an excess in the rates of major amputation; all other HBs had no significant variance between the rates of total major and minor amputations.

Figure 6.18 Major - Minor ratio for total amputation in 2008-2013 and 2013-2018 periods

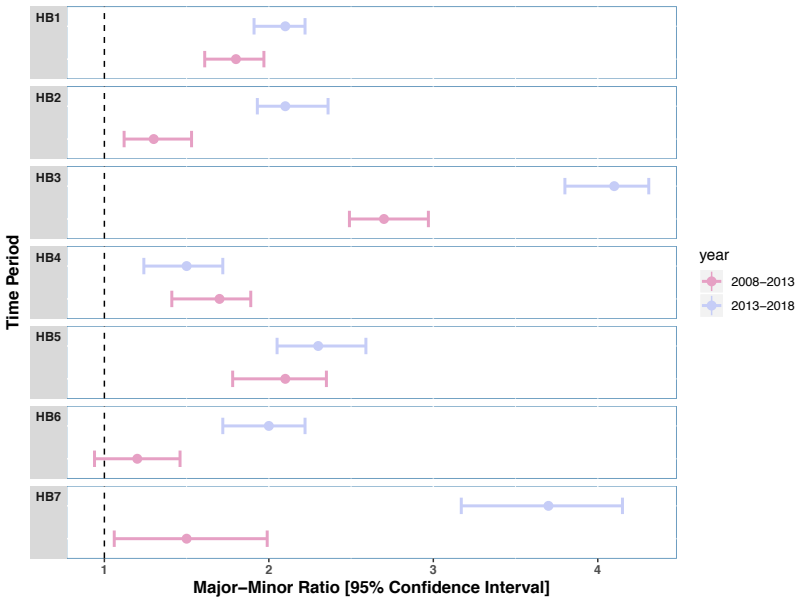
A-Total population



B- Non-Diabetes population



c- Diabetes Population



6.5 Discussion

This national study was performed to quantify the incidence and relative rate of amputation over the period of 2008 to 2018. The first aim of the study was to determine the trends in incident and total lower extremity amputation over the period. In all populations the crude number of major amputations fell across the period and the minor amputation rates increased although not as prominently in the population without diabetes. The first main objective of the chapter was to explore influence of diabetes on amputation within Wales. Despite the population with diabetes representing only 7% of the total population, over 50% of the incident amputations performed over the period were on persons with diabetes.

As expected directly standardised amputation rates in the population with diabetes were considerably higher compared to those in the population without diabetes. This was apparent across all amputation types and for incident and total amputations with particularly high standardised rates for minor amputations in men when compared to the non-diabetes population. When adjusted for age and sex, the incidence of incident major amputations in the male diabetes and non-diabetes population and in the female diabetes population decreased significantly over the period. There was no significant change in total or incident minor amputation rates for any population when looking at Wales as whole. The relative risk of any incident or total amputation between the diabetes and non-diabetes population did not change significantly over the study period. Amputation risk increased significantly with age in all population; age had a much greater effect on risk of amputation in the non-diabetes population. The risk for amputation of any type was higher in men than women.

Comparing the outcomes of this analysis to other published studies examining amputation rates is made difficult by variance in study design. A recent systematic review (Davies, Burdett, Bowling, Ahmad, & McClennon, 2019) highlighted the methodological differences in studies examining the epidemiology of lower limb amputations in England. There was variance in amputation definition, numerator type and denominator definition and use of standardisation of rates. If only crude rates are used it is not possible to make comparisons due to differences population structure. There was variance in the populations used to standardise resulting in marked variance in major lower extremity amputation prevalence from 3.0 to 76.1/100 000 PY in the whole English population and 0.7 to 332.4/100 000 PY in

the diabetes population. This study analysed incident amputation rate primarily as amputations are not independent events with initial amputation a significant predictor of future amputation (J. H. Lin, Jeon, Romano, & Humphries). As demonstrated in the HB section of this analysis, the HB with the highest incident rate of any incident amputation, HB1, also had the highest rate of total amputations and the greatest increase between the two. There was also greater variance between the HBs with the highest and lowest total amputation rates in both periods.

Major lower limb amputations are viewed as an adverse outcome of diabetes and are associated with poor survival rates and reduced quality of life. They are often used as a measure of quality of foot care services, as an outcome indicator for the comprehensive chain of service from prevention of foot problems to cardiovascular risk management and vascular surgical care. For the whole of Wales for the rolling period of 2016-2018 in the population with diabetes we found a total major amputation DSR of 6.7 [6.0-7.5]/10 000 PY. This was lower than the findings from the PHE diabetes foot care profile April 2019, which reported a DSR rate of 8.2/10 000 PY for the period of 2015/16 to 2017/18 in England. Interestingly, the crude rates of amputation in England also increased from the 2012/13-2014/15 period to the 2015/16-2017/18. However, when rates were standardised there was no significant change in rates. The reduction in age and sex standardised major amputation rate in the male and female population with diabetes could be seen as a positive indicator of improvement in services within Wales. It is suggestive that national campaigns such as the introduction of markers in QOF, annual audits and campaigns such as 'Putting Feet First' are having an effect in Wales. This, however, was not reflected in the findings in the non-diabetes population and when stratified by gender, specifically the female population. There are no studies from the UK that stratify amputation rates by gender with which to compare. Studies of the German population in 2008-2012 and 2005-2015 both found greater reductions in the major rate of amputation in women (Claessen et al., 2018; Spoden et al., 2019). This finding was mirrored in Finland between 1997-2007, where the rate reduction in women, especially in older age groups, was greater than in men. This was postulated to be through reduced rates of smoking (K. Winell et al., 2013a).

Women make up a greater proportion of the elderly population of Wales but even after age standardisation, the rate of risk reduction was not equal. Women have been found to have a higher rate of asymptomatic PVD (Schramm & Rochon, 2018). This can result in delayed diagnosis and missed opportunities for revascularisation, with women more likely to present with critical limb ischaemia. This study did not explore differences in revascularisation rates over the period and this would be an interesting area to explore and may explain the variance between genders and could be a contributing factor to the reduction in major amputation rates (Naseer Ahmad et al., 2014).

Men also have a higher rate of neuropathy and this, combined with a higher rate of amputation in general, may mean that services in Wales are targeted at men. This is reflected in findings of women having a lower rated self and health care related foot checks as seen in the last chapter and by Schramm et al (2018). There was a reduction in the rate of major amputation on year in women within the diabetes population. When stratified by area, in almost all HBs the greater reduction in major amputation rate was in the diabetes population. It could be that there are more interventions targeted towards the diabetes population in general, and women in the population with diabetes and men without diabetes were encompassed in these whilst engaging with services for diabetes annual review or symptomatic early-stage PVD respectively. These interventions wouldn't reach asymptomatic women who may have no engagement with health services. A higher mortality rate for both diabetes and non-diabetes related amputation has also been found in women which is suggested to be due to CVD, as men are younger at age of amputation (Morgan et al., 2000). This will be explored in the next chapter.

The disparity between the changes in minor-major amputation rate ratio between the genders also reflect a potential disparity within service provision. Minor amputations are often used as a preventative procedure to allow for removal of necrosis or infection source and allow for tissue healing. Minor-major amputation rate ratio has been used as an indicator of quality of foot care in previous epidemiological studies (K. Winell et al., 2013a; James S. Wrobel, Robbins, & Armstrong, 2006) with changes in minor-major ratios suggestive of a movement towards preventative foot care. As the denominators are matched, they are removed from the calculation removing the need for standardisation and issues due to

standard population selection. Although the decrease in minor-major ratio for women was not significant over time, it was in stark comparison to the large increase in minor-major ratio for the male diabetes population. This could again indicate some disparity in the care between genders although this study did not consider other potential confounding factors, such as deprivation level, which may drive this disparity.

Directly standardised rates of total minor amputation were found to have increased significantly in England between the period of 2012/13-2014/15 and 2015/16-2017/18 from 20.4/10 000 PY to 21.4/10 000 PY (PHE, 2019). This was not reflected in the Welsh population with no significant change in total or incident amputations over the period and considerably lower total DSR rates of 15.8/10 000 PY [14.6-17.1] in 2013-15 and 15.9/10 000 PY [14.7-17.2] in the 2016-2018 period. Although the rates of both major and minor amputation are lower in the Welsh population in this study, the minor-major ratios are similar to the PHE analysis. This could reflect the effect of national campaigns. In England rates of major amputation have been found to be at least 6 fold higher than in Wales (Naseer Ahmad et al., 2016). In our study relative risk of major amputation associated with diabetes was higher than that reported in the PHE analysis at 8.0 [7.9-8.1] over the period but in the literature the relative risk of amputation associated with diabetes for England has been reported as ranging between 7.4 and 41.3 . The variation can be explained by differences in study design and definitions used, making comparison difficult. Despite this, rates of amputation are still considerably higher within the diabetes population and with the consensus that most major amputations in patients with diabetes are preventable, the slow decline in incident amputation rate in this population is concerning. Within chapter 3 it was identified that fewer patients undergoing major amputation within the Swansea locality had undergone revascularisation procedures than would be expected and this would be an area to explore in future studies.

The second objective of the study was to examine the variance in amputation rates between areas in Wales. There was clear heterogeneity across the HBs within Wales with incident and total amputation rates varying by up to 80 and 100% respectively. This was true across all amputation types, populations and over time. As predicted the HB with the highest amputation rate in the diabetes population also had the highest amputation rate in the non-

diabetes population for all amputation types and over time suggesting that there could be differences within systems affecting all populations. Despite this, changes within HBs in amputation rates were often driven by changes in different populations at different times. The differences need to be explored further, controlling for factors such as deprivation and rates of peripheral vascular disease and access to revascularisation within the HBs that may be driving the variance before conclusions on health care can be drawn. The findings for the whole of Wales on major and minor ratio and the risk associated with having diabetes were reflected in every HB but to varying degrees. HB3 had the highest major-minor ratio in both periods and the lowest major amputation rate of the HBs for people with diabetes and HB7 had the lowest minor-major ratio for the non-diabetic population and was one of the only non-diabetes population with a significant major amputation increase. This again suggests that minor amputation can be used as a preventative strategy.

A strength of the study was the use of the SAIL databank to identify people with diabetes as it was possible to use primary, secondary and prescription data to classify patients. In the majority of studies from England an ICD-10 code at time of amputation were used to identify diagnosis of diabetes, or one data source or whole population QOF data was used which meant age and sex specific rates of diabetes had to be stratified. This could lead to an underestimation of the denominator and an inflated crude and standardised LEA rate. The use of an accurate algorithm for diagnosis of diabetes with an adequate lookback period could explain the lower major and minor amputation rates.

In summary, this chapter describes that major amputation rates declined in the population with diabetes over the 11-year period but this decline was small and was not reflected in the population without diabetes. We also identified that the amputation rates for both diabetes and non-diabetes populations varied significantly between HBs suggestive that there are differences in the extent and prevalence of driving factors to amputation within each area. Further investigation is required to explore disparities in rates of change between the genders, HBs and if an increased rate of minor amputation reduces rates of major amputation when controlling for factors that may confound the association

6.6 Limitations

An increased incidence of diabetes may explain some of the reduction in amputation incidence rate, as major amputation is an end-stage process and an increase in the number of newly diagnosed, relatively healthy patients within the denominator may mean the rates do not reflect a true reduction in amputation rate. The use of the whole Welsh population for standardisation partially protects against bias caused by a rapidly increasing diabetic population (Schofield et al., 2009).

Individuals with missing ALF-PE and missing WOB were not used in the study as it was not possible to verify records within SAIL; although the number was small it may be possible that some amputations were not included. HB could not be determined for some patients and the numbers used in the HB analysis were smaller. It was also not possible to determine if addresses were missing from each HB equally so this may have introduced some bias.

No adjustment was made for history of cardiovascular or cerebrovascular disease or rates of prior peripheral vascular disease or endovascular intervention, well known risk factors for LEA. However, there has been no significant change in the rate of CVD over the period suggesting this would not have an effect on the time trend for lower extremity amputation(British Heart Foundation, 2018). Furthermore, the aim of this chapter was to assess the incidence of amputation over the period 2008-2018 and assess for change in time trend over the period.

CHAPTER SEVEN

A Wales population-based approach to examine mortality following amputation in people with and without diabetes using the SAIL database

7.1 Introduction

As discussed, and examined in the chapter 6, amputation rates for populations with and without diabetes are known to vary by geographic location. This is true across the nations of the UK and within the HBs of Wales. Differences in incidence of amputation are dependent on the geographical area, healthcare structure, patient demography and patient's engagement with services. As well as variance in amputation rate between geographic locations, a variance in mortality following major amputation has also been documented (Fortington et al., 2013; Sargen, Hoffstad, & Margolis, 2013). A high mortality rate is associated with lower extremity amputation and is to be expected as the population undergoing amputation are often frail, multi-morbid and as a low predicted life expectancy can be used as an indication for major amputation by operating physicians when management of the diabetic foot is being considered (Thorud et al., 2016). Even with acceptance of considerable expected mortality there is variance in reported mortality rates. As with amputation incidence, direct comparison of mortality rates following amputation can be difficult due to differences in population, amputation definitions and reporting. With variability in mortality between populations previously reported, for future healthcare planning it is important to investigate mortality within Wales.

The impact of the morbidity and mortality in the population with diabetes where foot disease progresses to the point of amputation is substantial (Diabetes UK, 2018b). In people with diabetes in England, the median survival after amputation of any cause has been reported to be 20 months shorter compared to people without diabetes and five-year mortality rates after amputation are reported to be as high as 80% (Scott et al., 2014). Even those people who develop foot ulcers that do not progress to amputation have an approximate twofold increased risk of death compared to the diabetic population without ulcer (Robbins et al., 2008).

As highlighted in the last chapter, the incidence of amputation within the populations with and without diabetes within Wales varies between health boards and with some of this variance potentially due to disparities in population, and healthcare provision it is important to explore if these differences translate into variance in mortality.

Major amputation is viewed as an adverse outcome of diabetes, the result of the end stages of a disease process, whereas minor amputations are viewed as a treatment; a procedure to remove infection and necrosis with the aim of encouraging wound healing (PHE, 2019). With this view of the procedures, mortality would be expected to be lower in those undergoing only minor amputation in the populations with and without diabetes. It is expected that these patients will recover from the procedure, as it is intended to prevent the requirement for major amputation. Currently there are few studies within the literature reporting mortality following minor amputation for populations with and without diabetes. As rates of minor amputations are increasing within the population with diabetes in Wales it is pertinent to understand the mortality following this procedure as well as the mortality following major amputation.

7.2 Aims and Objectives

7.2.1 Aims

The specific aims of the chapter are to:-

(i) Determine the 30 day, 1-year and 5-year mortality rates following incident major and incident minor amputation in the Welsh diabetes and non-diabetes population between 2006-2013.

(ii) Explore the time dependent impact of diabetes on mortality rate while controlling for other risk factors for death including variance in health board.

(iii) Describe the main causes of death for the diabetes and non-diabetes population in those people who have undergone amputation.

7.3 Methods

7.3.1 Study population and data assessment

As described in the last chapter, data were extracted from SAIL, a secure anonymised information linkage databank (Lyons et al., 2009). This study primarily used clinical data from the WLGP, the PEDW and the OPDW. Nonclinical data were extracted from the ONS ADBE and ADDE as well as the WDSD. Any events, admissions or services received prior to December 2018 were included. All amputations between 2006-2013 were taken into account, regardless of cause in line with other national papers and PHE analysis (Naseer Ahmad et al., 2016; Claessen et al., 2018; PHE, 2019).

As described in the last chapter, people with diabetes were identified using an established algorithm (J. Rafferty et al., 2018; J Rafferty et al., 2021) utilising linked data from several clinical and non-clinical sources. People were considered to have diabetes from first registration of diabetes, those with gestational diabetes were excluded. Amputations were identified and classified as major or minor within PEDW using the methodology described in chapter 6.

The index date of entry into the study was the date of first minor or major amputation during the study period. Amputations were identified as incident using the methodology described in chapter six with at least a 5-year lookback period. All incident major and minor amputations between 2003-2013 were assessed and subjects followed until 2018-12-31 to give a minimum 5-year observation following amputation. If patients underwent both incident major and minor amputation during the study period, they were included in both analyses if minor amputation preceded major amputation.

7.3.2 Data collection and analysis

The primary variable of interest was time to death from date of admission for incident major or minor amputation. This date was classified as the index date. The date of death was taken from ONS ADDE. The ONS ADDE provides the date of death as recorded on the death certificate for all registered deaths in Wales, along with the recorded cause of death including

underlying cause of death. Time to death, in months, was calculated from index date to date of death. Records were censored at date of death or at the end of the follow-up period (2018-12-31), whichever occurred first.

Different socio-demographic factors and comorbidities that could reliably be sampled from hospital records were investigated as potential confounding factors. The factors included have been demonstrated to be associated with mortality in people with diabetes or associated with amputation within the diabetes and non-diabetes populations (Hoffstad, Mitra, Walsh, & Margolis, 2015; HSCIC, 2019). Independent characteristic variables included in both major and minor analysis were;- age at amputation, gender, WIMD quintile and health board at admission. Age was categorised into the age groups <65years, 65-75 years, 75-85 years and 85+ years as previous studies have demonstrated that mortality risk begins to increase in the population above the age of 65 years (Cascini et al., 2020; Gurney et al., 2018). Primary medical risk factors were selected as they were previously identified to be associated with the most frequent causes of death in the diabetes and PVD populations. Medical comorbidities included in both major and minor analysis were:- Charlson comorbidity index, a history of limb salvage procedures, HTN, ESRD, MI, CVA, congestive cardiac failure (CCF) and PVD. For the major amputation analysis amputation level, determined as AKA or BKA, was included. A history of subsequent major amputation within the study period was included for the minor amputation analysis.

The Chalrson comorbidity index is a tool, developed in 1987, that assesses diagnosis codes within hospital data that predict patient future morbidity and mortality (Armitage & van der Meulen, 2010). It combines 14 disease categories commonly associated with morbidity and mortality in hospital inpatients and is often used within epidemiological studies to estimate the frailty of a patient. For this study the updated Royal College of Surgeons (RCS) Charlson score was used (Armitage & van der Meulen, 2010). Codes pertaining to diabetes were not used in the score in this study as this was the variable defining the population not a co-morbidity. HIV/AIDS codes were not available within the data set and were not included in the analysis for either population. IDC10 codes for comorbidities within the index (Table 7.1) were identified from PEDW data up to one year prior to the index date and from the index admission.

Table 7.1 RCS Charlson morbidity index disease categories and ICD 10 codes (Armitage & van der Meulen, 2010)

Disease category	ICD-10 codes
AIDS/HIV infection	B20–B24
Any malignancy	C00–C26, C30–C34, C37–C41, C43, C45–C58, C60–C76, C80–C85, C88, C90–C97
Cerebrovascular disease	G45, G46, I60–I69
Chronic pulmonary disease	I26, I27, J40–J45, J46*, J47, J60–J67, J684, J701, J703
Congestive cardiac failure	I11, I13, I255, I42, I43, I50, I517
Dementia	A810, F00–F03, F051, G30, G31
Diabetes mellitus	E10–E14
Hemiplegia or paraplegia	G114, G81–G83
Liver disease	B18, I85, I864, I982, K70, K71, K721, K729, K76, R162, Z944
Metastatic solid tumour	C77–C79
Myocardial infarction	I21*, I22*, I23*, I252
Peripheral vascular disease	I70–I73, I770, I771, K551, K558, K559, R02, Z958, Z959
Renal disease	I12, I13, N01, N03, N05, N07, N08, N171*, N172*, N18, N19*, N25, Z49, Z940, Z992
Rheumatological disease	M05, M06, M09, M120, M315, M32–M36

*Indicates acute condition included only if present within hospital admission record within preceding year

All primary medical risk factors listed above, excluding ESRD, were identified from a 5 year look back period from the index date using ICD 10 codes (appendix V). ESRD was identified from inpatient admission codes using the standards described by the UK BIOBANK(UK Biobank, 2017a). Again, a 5 year look back period from index date was applied.

A previous limb salvage attempt by arterial bypass, angioplasty or a combination of both procedures was identified for each patient using coding methods described in previous papers examining PVD outcomes (P. W. Moxey et al., 2011b) (appendix V). A history of limb salvage was recorded if the procedures had occurred within a 2-year look-back period from the index date. The length of the look back period was adopted as the risk of amputation following attempted limb salvage and mortality associated with limb salvage has been shown to plateau

at two years (Darling et al., 2018). Progression to amputation or any effect on mortality associated with the procedure would less likely be related to the limb salvage attempt after that point.

A person's health board at entry into the study was derived using the method explained in chapter 6. from their registered home address at time of admission using 2011 LSOA unitary authorities. WIMD was derived from LSOA information derived from the patient's home address. (WIMD) (StatsWales, 2014). The WIMD score was split into quintiles from the most to the least deprived groups. Cause of death is presented from codes in the ADDE of the underlying cause of death in each case.

7.3.3 Statistical Analysis

All analysis was undertaken in R (R version 3.6.1 2019) and figures were produced using the package ggplot2(Wickham, 2016). For comparison of baseline variables between groups chi-squared and rank biserial correlation were used for categorical variables and the student t-test and Mann-Whitney U test for normally and non-normally distributed continuous variables respectively. For all analyses, a $p \leq 0.05$ was considered statistically significant. Characteristics of patients that died at 30 days, 1 year and 5 years were compared to those that survived at 5 years using chi-squared tests for categorical variables and t-test for continuous variables. Missing data was not imputed, the numbers included in analysis are noted throughout.

Survival was assessed with Kaplan-Meier curves and stratified log-rank tests were used to analyse differences in survival associated with independent variables. Crude differences between the diabetes and non-diabetes population for major amputation violated the proportional hazard assumption as the survival curves crossed, therefore, proportional hazards could not be assumed(Johnson & Shih, 2007). This was confirmed using the Schoenfeld test for proportional hazards. To allow for this, cox regression with a step function was performed using discrete time intervals to model the time dependency of diabetes whilst assessing for other predictors of death in the population.

In all models, death was the primary outcome and diabetes was the primary exposure variable. The analysis was stratified by amputation type (Major or Minor). Hazard ratios are presented individually for all variables with respect to mortality and then adjusted within each model. The first model included diabetes interaction with discrete time intervals (30 and 60 days, 6 months, and 1-, 2-, 3-, and 5 years), age and gender. The second model included Charlson index and surgical history, the third included medical risk factors for death and the fourth included geographical variance and socioeconomic deprivation.

7.4 Results

7.4.1 Population characteristics

7.4.1.1 Major amputations

Of the 2542 individuals who underwent incident major amputation between 2006-2013, 67.7% were men (n=1720), the mean age at amputation was 69 ±14.2 years and there was an even split of amputation level between AKA and BKA (AKA:BKA 49.3:50.7%) (Table 7.2). Marginally, more amputations were performed in patients without diabetes (51.6%). A greater proportion of the population with diabetes were men and were more likely to have undergone a BKA, have a history of HTN, ESRD, MI, CCF and PVD compared to the population without diabetes. Despite a higher rate of PVD they did not have a significantly greater history of a prior limb salvage procedure (diabetes 433 (35.2%): non-diabetes 432 (33.0%), p=0.24). When examining the population with PVD in isolation, a higher percentage of persons in the non-diabetes population underwent a revascularisation procedure (diabetes 41.1%: non diabetes 44.0%) but this different was not statistically significant. Persons with diabetes were also significantly more likely to have undergone more than 1 major amputation within the study period. There was no significant difference in the rates of prior CVA, in Charlson score or WIMD quintile between groups. There was a significant difference in the crude rates of people in each health board undergoing amputation in the population with and without diabetes.

Table 7.2 Characteristics of the population undergoing incident major lower extremity amputation, stratified by diabetes

Variable (n)	Total Population n= 2542	Diabetes Population n = 1231(48.4%)	Non-Diabetes Population n = 1311(51.6%)	
	n (%)	n (%)	n (%)	Pvalue
Level (2542)				
AKA	1253 (49.3)	472 (38.3)	781 (59.6)	**<0.001**
BKA	1289 (50.7)	759(61.7)	530 (40.4)	
Gender (2542)				
Men	1720 (67.7)	875 (71.1)	845 (64.5)	**<0.001**
Women	822 (32.3)	356 (28.9)	466 (35.5)	
Age (2540)	*mean (sd)*	*mean (sd)*	*mean (sd)*	
All	69 (14.2)	70 (11.5)	69 (16.3)	0.35
Men	68 (13.8)	69 (11)	67 (16.2)	0.46
Women	71 (14.6)	71(12.3)	72 (16.1)	0.51
WIMD (2490)	*n (%)*	*n (%)*	*n (%)*	
1	680 (26.8)	329 (26.7)	351 (26.8)	0.23
2	581 (22.9)	302 (24.5)	279 (21.3)	
3	463 (18.2)	207 (16.8)	256 (19.5)	
4	427 (16.8)	211 (17.1)	216 (16.5)	
5	337 (13.3)	163 (13.2)	174 (13.3)	
Charlson index (2542)				
0	1349 (53.1)	646 (52.5)	703 (53.6)	0.71
1	840 (33.0)	410 (33.3)	430 (32.8)	
2	305 (12.0)	148 (12.0)	157 (12.0)	
3+	35 (1.4)	27 (2.2)	21 (1.6)	
Medical history (2542)				
HTN	1624 (63.9)	961 (78.1)	663 (50.6)	**<0.001**
ESRD	122 (4.8)	91 (7.4)	31 (2.4)	**<0.001**
MI	408 (16.1)	257 (20.9)	151 (11.5)	**<0.001**
CVA	413 (16.2)	212 (17.2)	201 (15.3)	0.20
CCF	587 (23.1)	369 (30.0)	218 (16.6)	**<0.001**
PVD	2037 (80.1)	1054 (85.6)	983 (75.0)	**<0.001**
Surgical history (2542)				
Limb Salvage Procedure	865 (34.0)	433 (35.2)	432 (33.0)	0.24
>1 major LEA	514 (20.2)	294 (23.9)	220 (16.8)	**<0.001**
Health Board (2490)				
1	551 (21.7)	289 (23.5)	262 (20.0)	**<0.001**
2	416 (16.4)	220 (17.9)	196 (15.0)	
3	434 (17.1)	177 (14.4)	257 (19.6)	
4	331 (13.0)	176 (14.3)	155 (11.8)	
5	248 (9.8)	99 (8.0)	149 (11.4)	
6	403 (15.9)	190 (15.4)	213 (16.2)	
7	105 (4.1)	61 (5.0)	44 (3.4)	

Comparison of age by gender: men with diabetes vs women with diabetes p=0.77; men without diabetes versus women without diabetes **p<0.001**

7.4.1.2 Minor Amputation

Two thousand and seventy-seven individuals underwent minor amputation between 2006-2013. Again, the majority of amputations occurred in men (1865, 64.8%) and the mean age at amputation was lower than that seen for major amputation at 68 ±14.5 years (Table 7.3). A greater proportion of the amputations were performed in the population with diabetes (55.5%). In the diabetes population with a significantly higher proportion of those undergoing amputation were men and they were more likely to have a diagnosis of HTN, ESRD, MI, CCF, PVD and CVA. A higher proportion of persons with diabetes went on to have a major amputation within the study period. Unlike in the major amputation analysis, there was a significant difference in the number of limb salvage procedures performed prior to amputation. However, when analysing the population with PVD alone significantly fewer persons with diabetes received a prior revascularisation procedure compared to those without (diabetes 40.9%: non-diabetes 49.6%, $p<0.001$). There was a significant difference in the percentage of people within each WIMD quintile between those with and without diabetes. There was no significant difference in the percentage of each population within each health board or difference in Charlson score between each group.

Table 7.3 Characteristics of the population undergoing incident minor lower extremity amputation, stratified by diabetes

Variable (n)	Total Population n= 2877	Diabetes Population n= 1596 (55.5%)	Non Diabetes Population n = 1281 (44.5%)	
	n (%)	n (%)	n (%)	P value
Gender (2877)				
Men	1865 (64.8)	1196 (74.9)	669 (52.2)	**<0.001**
Women	1012 (35.2)	400 (25.1)	612 (47.8)	
Age (2875)	*mean (sd)*	*mean (sd)*	*mean (sd)*	
All	68 (14.5)	67 (12.7)	68 (16.4)	0.22
Men	66 (14.3)	67 (12.2)	66 (17.4)	0.20
Women	70 (14.5)	69 (13.9)	70 (14.9)	0.10
WIMD (2818)	*n (%)*	*n (%)*	*n (%)*	
1	641 (22.3)	394 (24.7)	247 (19.3)	**<0.001**
2	643 (22.3)	347 (21.7)	296 (23.1)	
3	579 (20.1)	342 (21.4)	237 (18.5)	
4	507 (17.6)	257 (16.1)	250 (19.5)	
5	445 (15.5)	222 (13.9)	223 (17.4)	
Charlson index (2877)				
0	1973 (68.6)	1105 (69.2)	868 (67.8)	0.80
1	700 (24.3)	377 (23.6)	323 (25.2)	
2	185 (6.4)	103 (6.5)	82 (6.4)	
3+	19 (0.7)	11 (0.7)	8 (0.6)	
Medical History (2877)				
HTN	1689 (58.7)	1134 (71.1)	555 (43.3)	**<0.001**
ESRD	122 (4.2)	103 (6.5)	19 (1.5)	**<0.001**
MI	293 (10.2)	212 (13.3)	81 (6.3)	**<0.001**
CVA	249 (8.7)	156 (9.8)	93 (7.3)	**0.02**
CCF	415 (14.4)	301 (18.9)	114 (8.9)	**<0.001**
PVD	1688 (58.7)	1134 (71.1)	554 (43.2)	**<0.001**
Surgical History (2877)				
Limb Salvage Procedure	739 (25.7)	464 (29.1)	275 (21.5)	**<0.001**
Major LEA	577 (20.1)	439 (27.5)	138 (10.8)	**<0.001**
Health Board (2818)				
1	619 (21.5)	345 (21.6)	274 (21.4)	0.72
2	484 (16.8)	270 (16.9)	214 (16.7)	
3	625 (21.7)	337 (21.1)	288 (22.5)	
4	348 (12.1)	192 (12.0)	156 (12.2)	
5	275 (9.6)	166 (10.4)	109 (8.5)	
6	321 (11.2)	176 (11.0)	145 (11.3)	
7	146 (5.1)	78 (4.9)	68 (5.3)	

Comparison of age by gender; men with diabetes vs women with diabetes **p=0.009**; men without diabetes versus women without diabetes **p <0.001**

7.4.2 Mortality

7.4.2.1 Major amputations

Overall, 1934 (76.1%) people died over the follow-up period, 235 (9.2%) within 30 days, 817 (32.1%) within 1 year and 1573 (61.9%) within 5 years. Of those who died, 52.5% (n=1015) had a diagnosis of diabetes. The median survival time was 36.5 [35.9-39.0] months (Table 7.4). People undergoing AKA had a significantly shorter survival time of 23.2 [19.6-27.8] months compared to those undergoing BKA (52.2 [47.4-58.4] months, p<0.001) (Figure 7.1). Significant differences were seen by gender (Figure 7.2), age (Figure 7.3), and when amputation level was stratified by age. Survival time following amputation for every age group was significantly shorter for those undergoing AKA. The greatest difference in survival time between AKA and BKA was seen in those under 65 years of age at time of amputation. People in the under 65 years age group who required an AKA had a 31.5 month shorter average survival time compared to those that underwent a BKA (BKA 101.1 [84.2-121] months: AKA 69.9 [46.2-87.4] months).

Figure 7.4 shows the Kaplan-Meier curves demonstrating the difference in survival following amputation stratified by diabetes diagnosis. Overall, 919 (70.1%) people without diabetes died over the follow-up period, 138 (10.5%) in the first 30 days, 421 (32.1%) within 1 year and 749 (57.1%) within 5 years. In the population with diabetes 1015 (82.5%) people died over the period, 97 (7.9%) in the first 30 days, 396 (32.2%) in the first 30 days and 825 (67.0%) within 5 years. The population without diabetes had a median survival of 43.8 [37.3-48.0] months, over 10 months longer than those with diabetes (31.3 months [29.0-35.7]). In the first 30 days a smaller percentage of people with diabetes died (7.9%). This trend then reversed just prior to 1-year following amputation and the survival curves for the two populations crossed. At five years a greater proportion of the population with diabetes had died. The relative mortality risk associated with diabetes in univariate analysis was time dependent with greater survival for those with diabetes for the first year after major amputation. There was no difference in mortality at 365 days, with a mortality of 32% in both populations.

Table 7.4 Crude rates of cumulative percentage of persons undergoing major lower extremity amputation that died at 30 day, 1 and 5 years

									Survival	(months)	
Variable (n)	N	n died	30-days	%	1-year	%	5-year	%	Median	95% CI	P value
All (2542)		1934	235	9.2	817	32.1	1573	61.9	36.5	[35.9-39.0]	
Level											
BKA	1289	905	65	5.0	307	23.8	694	53.8	52.2	[47.4-58.4]	**<0.001**
AKA	1253	1029	170	13.6	510	40.7	879	70.2	23.2	[19.6-27.8]	
Gender											
Men	1720	1274	137	8.0	530	30.8	1032	60.0	38.5	[34.5-43.3]	**<0.001**
Women	822	660	98	11.9	287	34.9	541	65.8	33.5	[28.7-38.8]	
Age											
<65	863	456	45	5.2	149	17.3	351	40.7	87.8	[76.8-106.1]	**<0.001**
65-74	695	570	65	9.4	220	31.7	434	62.4	38.4	[33.0-44.1]	
75-84	665	608	79	11.9	290	43.6	516	77.6	17.4	[13.8-22.3]	
85+	319	300	46	14.4	158	49.5	272	85.3	12.3	[8.2-16.2]	
Diabetes											
No	1311	919	138	10.5	421	32.1	749	57.1	43.8	[37.3-48.0]	
Yes	1231	1015	97	7.9	396	32.2	825	67.0	31.3	[29.0-35.7]	
Age and Level											
BKA											
<65	566	287	16	2.8	72	12.7	211	37.3	101.1	[84.2-121.0]	**<0.001**
65-74	349	283	15	4.3	81	23.2	197	56.4	51.0	[40.5-59.1]	
75-84	277	243	24	8.7	107	38.6	205	74.0	23.8	[17.0-30.4]	
85+	97	92	10	10.3	47	48.5	81	83.5	12.4	[7.4-28.2]	
AKA											
<65	297	169	29	9.8	77	25.9	140	47.1	69.6	[56.2-87.8]	
65-74	346	287	50	14.5	139	40.2	237	68.5	28.8	[19.6-37.1]	
75-84	388	365	55	14.2	183	47.2	311	80.2	13.9	[10.4-20.2]	
85+	222	208	36	16.2	111	50.0	191	86.0	12.0	[7.5-16.6]	

AKA: Above knee amputation; BKA: Below Knee amputation. P is log rank between categories for median survival time. Not calculated for diabetes status.

Figure 7.1 - Crude Kaplan- Meier survival curves after incident major amputation stratified by amputation level

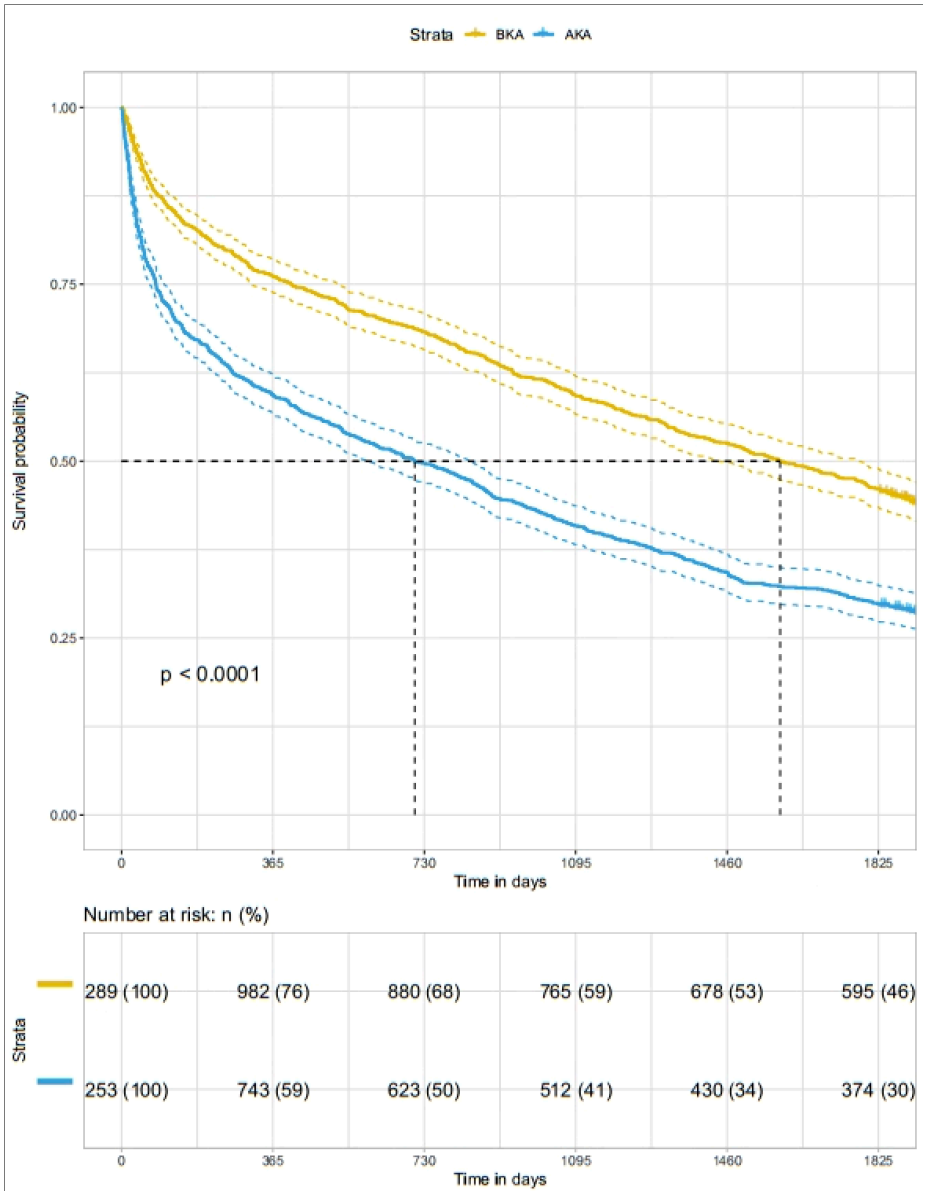


Figure 7.2- Crude Kaplan- Meier survival curves after incident major amputation stratified by gender

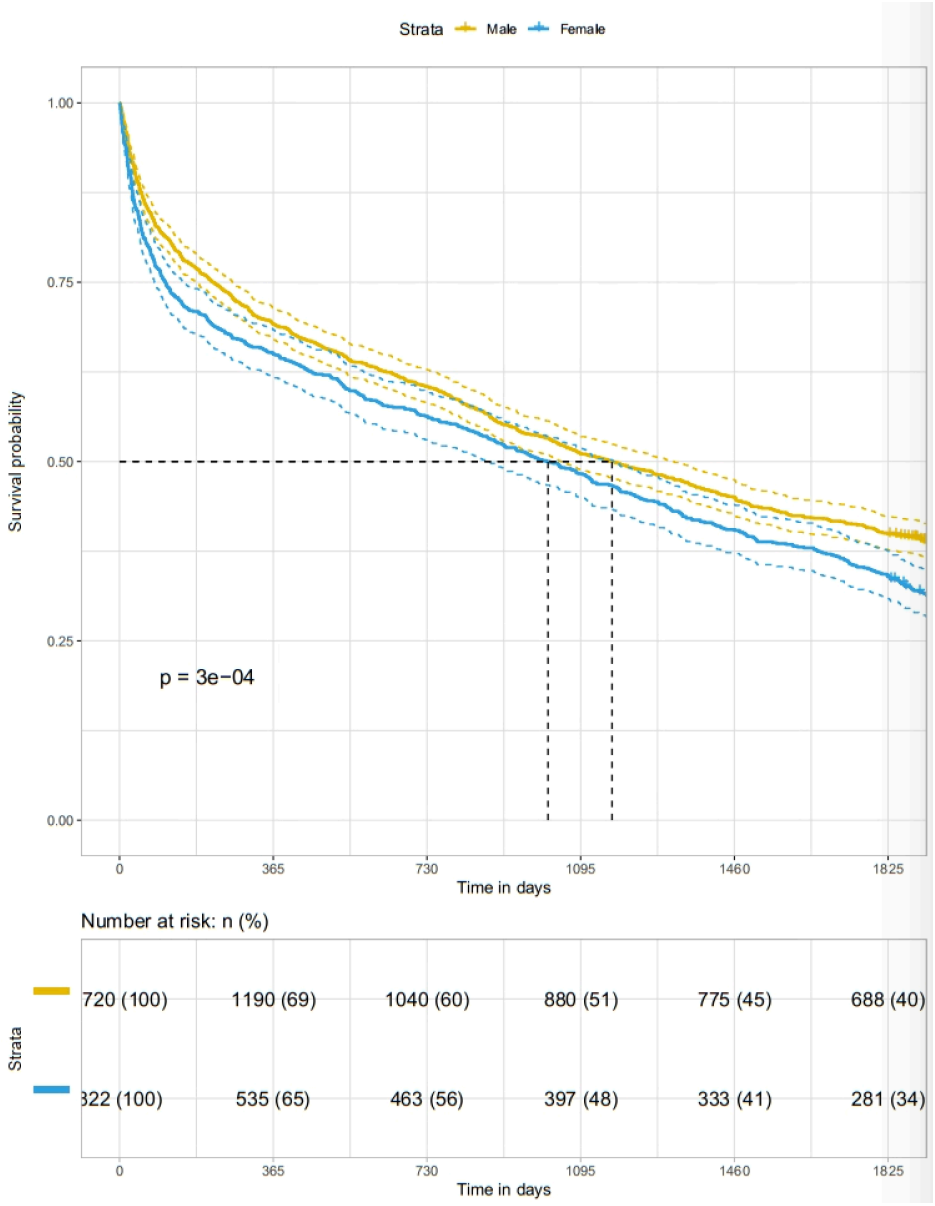


Figure 7.3 - Crude Kaplan- Meier survival curves after incident major amputation stratified by age categories

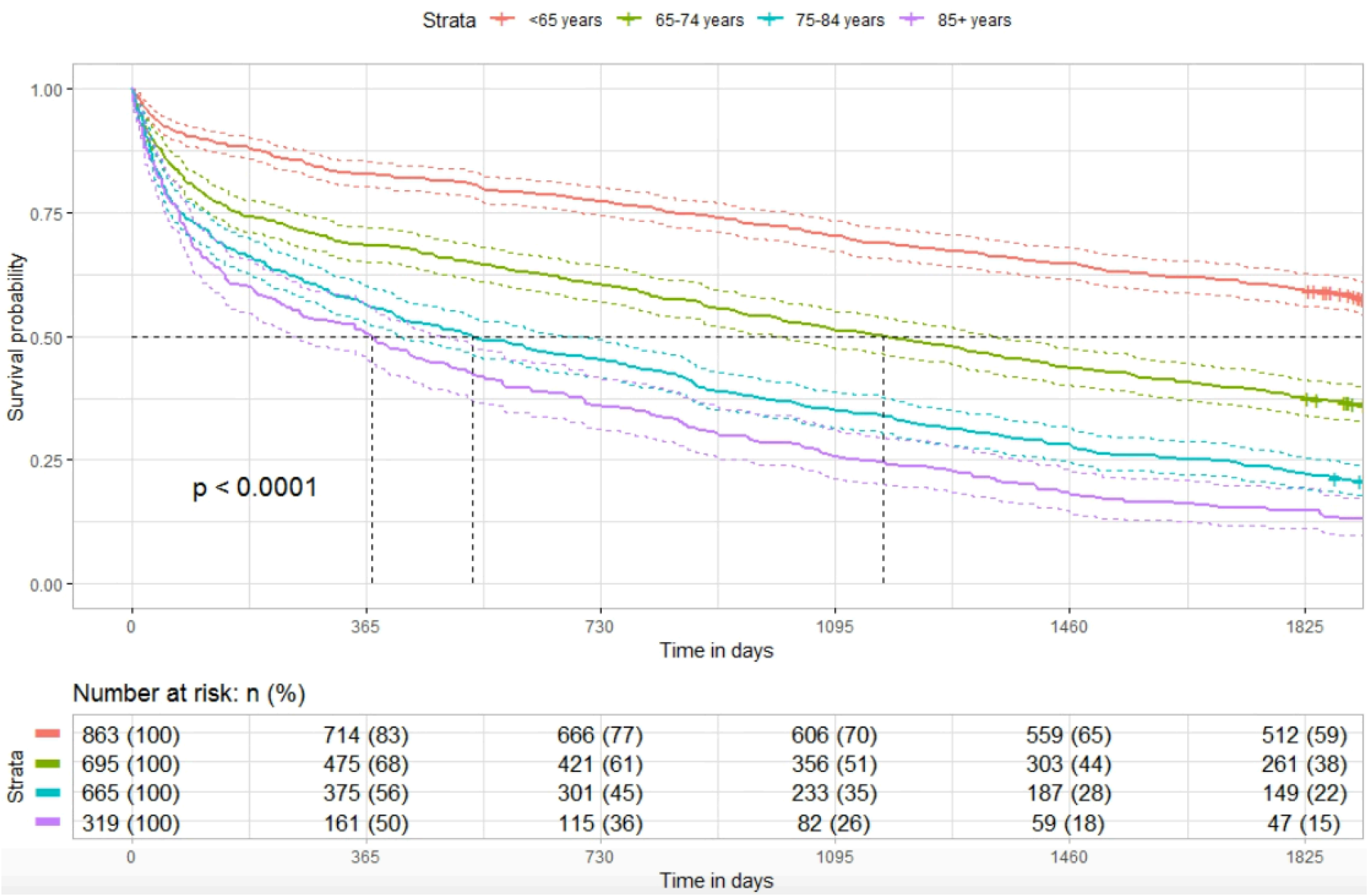
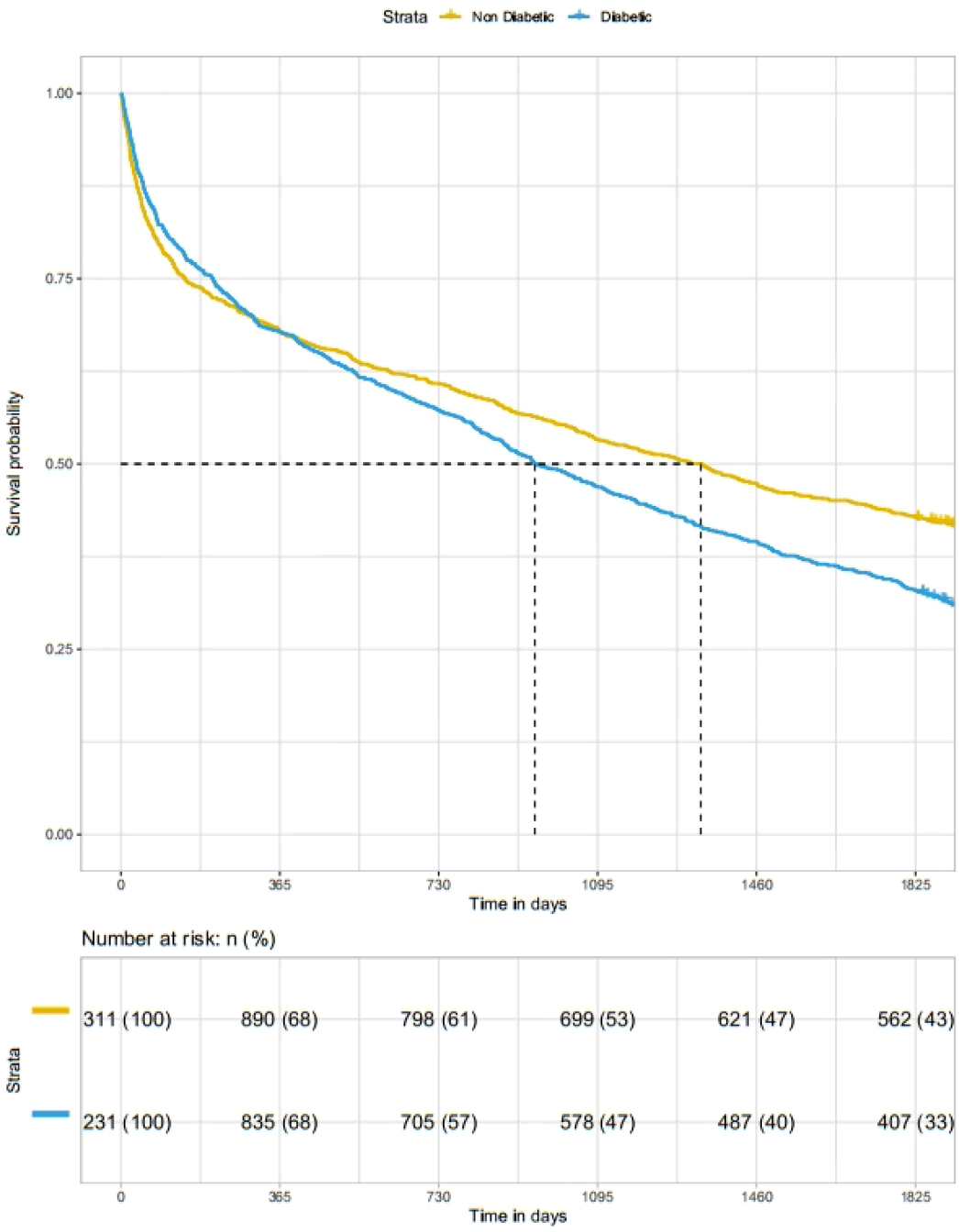


Figure 7.4 Crude Kaplan-Meier survival curves after incident major lower extremity amputation stratified for history of diabetes



The results of all cox regression analysis models for major amputation are shown in Table 7.4. In the unadjusted model there was a significant relative mortality risk associated with diabetes in all time periods except for between 60 days and 6 months. Between 0-30 days the relative mortality risk associated with diabetes was negative at 0.75 [0.58-0.97] , after 6 months it had become positive at 1.45 [1.08-1.94]. The relative risk of mortality associated with diabetes increased to a maximum of 1.62 [1.29-2.02] between years 3-5. In the univariate analysis, individually, increasing age, female gender, increasing Charlson index, AKA compared to BKA and a history of any of the medical risk factors were all associated with an increased risk of mortality. A Charlson index score of 3 or more compared to a score of 0 inferred the greatest risk, with a hazard ratio of 4.24 [3.17-5.69]. A history of a limb salvage procedures or a decreasing WIMD score had no significant effect on the risk of mortality. There was no significant difference in mortality risk between health boards.

In the first model, adjusted for age, sex and gender, the relative mortality risk for diabetes was significant at 6 months to 1 year: 1.46 [1.09-1.96]; at 1 to 2 years: 1.53 [1.17-2.00]; at 2 to 3 years: 1.48 [1.14-1.92]; at 3 to 5 years: 1.53 [1.22-1.91]. Increasing age remained significantly associated with mortality but when controlling for age and diabetes status, female gender was not found to be. The most parsimonious model for incident major amputation was model 3 which included diabetes status, gender, Charlson index, surgical history and the other medical risk factors. Model 3 was taken as the fully adjusted model as inclusion of WIMD quintile and geographical location had no effect on the hazard ratios or the predictive value of the model. The concordance statistic for both model 3 and model 4 0.70 [$\sigma\bar{x}$ 0.006] predicting 70% of mortality that occurred. Neither WIMD or geographical location were significantly associated with mortality in the unadjusted or in any adjusted model.

In the fully adjusted model the hazard ratios associated with diabetes were maintained with an increased risk of mortality seen after the first 6 month following amputation. The reduction of risk of mortality associated with diabetes in the time period between 0 and 30 days remained statistically significant; HR 0-30 days: 0.74 [0.57-0.96]. There was no association between diabetes and mortality in the time period between 60 days and 6 months after amputation. Increasing age remained significantly associated, increasing the risk of mortality

(HR 1.04 [1.03-1.04] per year). As did increasing Charlson index score (score 1, 1.39 [1.25-1.55]; 2, 1.76 [1.50-2.07]; 3+, 2.30[1.66-3.18]), a history of ESRD (2.35[1.92-2.87]), MI (1.21[1.07-1.37]), CCF (1.17[1.03-1.32]) and PVD (1.42[1.24-1.63]) and having an AKA (1.24[1.13-1.37]). A history of a limb salvage procedure within the 2 years prior to LEA admission was associated with a reduction in risk of mortality with a hazard ratio of 0.83 [0.76-0.92]. This was the only variable associated with reduced risk of mortality.

When the analysis was stratified by level of amputation, Model 3 was the most parsimonious model in the AKA analysis. Inclusion of WIMD and geographical location again had no effect on the hazard ratios or on the concordance statistic. Neither of these variables were significantly associated with mortality. Diabetes was not shown to be significantly associated with mortality in any time period. There was a trend towards an increased risk of mortality over time but this was not statistically significant. All other independent variables that had associations with mortality in the unstratified analysis remained significant apart from history of MI. A history of limb salvage procedure was the only variable associated with a reduction in the risk of mortality.

In the stratified analysis exploring BKA model 4, the model with all variables included, was the most parsimonious and had the highest concordance statistic at 0.73 $\sigma\overline{x}$ 0.008. In this analysis there was a statistically significant association between amputation and deprivation. Increasing WIMD quintile was associated a decreasing risk of mortality when controlling for other variables. Compared to the most deprived quintile, patients in the least deprived quintile (WIMD quintile 5) were 21% less likely to die at any time point within the follow up period (HR 0.79 [0.63-0.99]). A trend towards reduced risk was seen in the other quintiles when compared to quintile 1 but none were statistically significant. The reduction in risk of mortality for the population with diabetes in the time period between 0 and 30 days was statistically significant for BKA (HR 0.61 [0.38-0.99]). There was an increased risk of death for the time periods over 1 year, with the greatest risk associated with diabetes seen between 3 to 5 years (HR 1.73 [1.24-2.43]). All other independent variables that had associations with mortality in the unstratified analysis remained significant apart from history of CCF. A history of a prior limb salvage procedure inferred a greater reduction in risk of mortality than in the unstratified analysis with a HR of 0.81 [0.70-0.93].

Table 7. 5 Result of Cox regression model analysis of predictors for mortality after incident major amputation

	Full cohort				AKA				BKA				
Covariate	Unadjusted	model 1	model 2	model 3	unadjusted	model 1	model 2	model 3	unadjusted	model 1	model 2	model 3	model 4
Diabetes													
0-30 days	**0.75***	1.00	0.82	**0.74***	0.99	1.01	0.99	0.93	0.75	0.72	0.71	**0.62****	**0.61****
	[0.58-0.97]	[0.62-1.02]	[0.63-1.05]	**[0.57-0.96]**	[0.73-1.35]	[0.74-1.37]	[0.73-1.35]	[0.69-1.27]	[0.47-1.21]	[0.45-1.16]	[0.44-1.13]	**[0.38-0.99]**	**[0.38-0.99]**
30-60 days	0.87	0.91	0.94	0.85	1.07	1.08	1.06	0.99	0.95	0.90	0.88	**0.76***	**0.75***
	[0.64-1.30]	[0.67-1.25]	[0.68-1.29]	[0.62-1.1]	[0.72-1.60]	[0.72-1.61]	[0.71-1.58]	[0.66-1.49]	[0.55-1.62]	[0.53-1.55]	[0.52-1.50]	**[0.44-1.30]**	**[0.44-1.29]**
60-6	1.02	1.04	1.07	0.97	1.00	0.98	0.96	0.89	1.39	1.32	1.30	1.12	1.12
month	[0.79-1.31]	[0.81-1.35]	[0.83-1.38]	[0.75-1.25]	[0.71-1.41]	[0.70-1.39]	[0.67-1.34]	[0.63-1.26]	[0.02-2.11]	[0.87-2.00]	[0.85-1.97]	[0.73-1.71]	[0.73-1.71]
6-12	**1.45****	**1.46****	**1.51****	**1.37***	1.45	1.40	1.35	1.27	**1.85****	**1.73***	**1.74***	1.52	1.52
month	**[1.08-1.94]**	**[1.09-1.96]**	**[1.12-2.02]**	**[1.02-1.83]**	[0.98-2.16]	[0.94-2.08]	[0.91-2.00]	[0.85-1.89]	**[1.15-2.97]**	**[1.08-2.77]**	**[1.08-2.79]**	[0.94-2.45]	[0.94-2.45]
1-2 years	**1.53*****	**1.53****	**1.56****	**1.43****	**1.55***	**1.51***	1.41	1.33	**2.08****	**1.87****	**1.88****	**1.67***	**1.65****
	[1.17-2.00]	**[1.17-2.00]**	**[1.20-2.05]**	**[1.09-1.87]**	**[1.08-2.22]**	**[1.05-2.16]**	[0.99-2.02]	[0.93-1.91]	**[1.34-3.23]**	**[1.20-2.90]**	**[1.21-2.92]**	**[1.07-2.59]**	**[1.10-2.57]**
2-3 years	**150*****	**1.48****	**1.51****	**1.39***	**1.47***	1.42	1.34	1.26	**1.86****	**1.65***	**1.65***	1.47	**1.49***
	[1.16-1.95]	**[1.14-1.92]**	**[1.16-1.96]**	**[1.07-1.81]**	**[1.01-2.15]**	[0.98-2.07]	[0.92-1.95]	[0.86-1.84]	**[1.25-2.75]**	**[1.11-2.44]**	**[1.11-2.44]**	[0.98-2.18]	**[1.00-2.23]**
3-5 years	**1.62*****	**1.53*****	**1.58*****	**1.46****	1.26	1.20	1.15	1.08	**2.31*****	**1.95*****	**1.94*****	**1.75****	**1.73****
	[1.29-2.02]	**[1.22-1.91]**	**[1.26-1.98]**	**[1.16-1.83]**	[0.89-1.78]	[0.85-1.70]	[0.81-1.62]	[0.76-1.53]	**[1.66-3.22]**	**[1.40-2.72]**	**[1.39-2.71]**	**[1.25-2.44]**	**[1.24-2.43]**
Age	**1.04*****	**1.04*****	**1.04*****	**1.04*****	**1.04*****	**1.04*****	**1.03*****	**1.03*****	**1.05*****	**1.05*****	**1.04*****	**1.04*****	**1.05*****
	[1.04-1.05]	**[1.04-1.05]**	**[1.03-1.04]**	**[1.03-1.04]**	**[1.03-1.04**	**[1.03-1.04]**	**[1.03-1.04]**	**[1.03-1.04]**	**[1.04-1.05]**	**[1.04-1.05]**	**[1.04-1.05]**	**[1.04-1.05]**	**[1.04-1.05]**
Women	**1.19*****	1.00	1.00	1.03	**1.15***	0.97	0.96	1.02	1.09	1.01	1.02	1.08	1.08
	[1.08-1.31]	[0.91-1.10]	[0.91-1.10]	[0.93-1.13]	**[1.02-1.30]**	[0.85-1.10]	[0.85-1.10]	[0.89-1.16]	[0.94-1.26]	[0.87-1.17]	[0.88-1.18]	[0.93-1.25]	[0.93-1.25]
Charlson score													
0	ref		ref	ref	ref		Ref	ref	ref		ref	ref	ref
1	**1.80*****		**1.53*****	**1.39*****	**1.67*****		**1.55*****	1.42	**1.80*****		**1.51*****	**1.38*****	**1.42*****
	[1.63-1.99]		**[1.38-1.69]**	**[1.25-1.55]**	**[1.47-1.93]**		**[1.35-1.77]**	[1.22-1.65]	**[1.56-2.08]**		**[1.30-1.75]**	**[1.17-1.62]**	**[1.20-1.67]**
2	**2.70*****		**2.04*****	**1.76*****	**2.12*****		**1.82*****	1.56	**3.29*****		**2.43*****	**2.31*****	**2.20*****
	[2.36-3.09]		**[1.78-2.33]**	**[1.50-2.07]**	**[1.78-2.54]**		**[1.52-2.18]**	[1.26-1.93]	**[2.67-4.05]**		**[1.97-3.00]**	**[1.81-2.96]**	**[1.72-2.81]**
3+	**4.24*****		**3.13*****	**2.30*****	**3.53*****		**3.14*****	2.30	**4.75*****		**2.95*****	**2.43*****	**2.32*****
	[3.17-5.69]		**[2.33-4.20]**	**[1.66-3.18]**	**[2.43-1.13]**		**[2.16-4.56]**	[1.52-2.49]	**[2.96-7.64]**		**[1.83-4.76]**	**[1.88-1.34]**	**[1.35-4.00]**
AKA	**1.58*****		**1.23*****	**1.24*****	-			-	-		-	-	-
	[1.42-1.70]		**[1.12-1.36]**	**[1.13-1.37]**									
Limb	1.00	-	0.92	**0.85*****	**0.86***		0.89	**0.85 ***	**1.17***		0.93	**0.83***	**0.81****
salvage	[0.91-1.09]		[0.83-1.00]	**[0.77-0.93]**	**[0.76-0.98]**		[0.79-1.02]	**[0.74-0.97]**	**[1.02-1.34]**		[0.81-1.06]	**[0.72-0.95]**	**[0.70-0.93]**
HTN	**1.67*****			0.97	**1.34*****			0.92	**2.16*****			1.08	1.05
	[1.51-1.84]			[0.87-1.08]	**[1.17-1.52]**			[0.80-1.05]	**[1.86-2.50]**			[0.91-1.27]	[0.89-1.24]
ESRD	**1.92*****			**2.35*****	**2.17*****			**2.40*****	**2.26*****			**2.39*****	**2.45*****
	[1.59-2.32]			**[1.93-2.87]**	**[1.53-3.07]**			**[1.67-3.44]**	**[1.78-2.85]**			**[1.88-3.03]**	**[1.92-3.12]**
MI	**1.68*****			**1.21****	**1.44*****			1.14	**1.93*****			**1.36*****	**1.34****

	[1.50-1.88]	**[1.07-1.37]**	**[1.23-1.69]**	[0.97-1.35]	**[1.63-2.28]**	**[1.14-1.63]**	**[1.11-1.61]**
CVA	**1.72*** **	1.13	**1.44*** **	1.15	**1.92*** **	1.08	1.07
	[1.54-1.93]	[0.99-1.28]	**[1.24-1.66]**	[0.97-1.35]	**[1.59-2.31]**	[0.88-1.34]	[0.87-1.33]
CCF	**2.08*** **	**1.17***	**1.86*** **	**1.25****	**2.24*** **	1.00	1.08
	[1.88-2.30]	**[1.03-1.32]**	**[1.62-2.13]**	**[1.06-1.46]**	**[1.93-2.60]**	[0.83-1.21]	[0.88-1.30]
PVD	**2.09*** **	**1.42*** **	**1.71*** **	**1.35****	**2.49*** **	**1.51*** **	**1.47*** **
	[1.84-2.38]	**[1.24-1.63]**	**[1.43-2.03]**	**[1.12-1.63]**	**[2.06-3.01]**	**[1.23-1.86]**	**[1.20-1.81]**
WIMD							
1	ref		ref		ref		ref
2	0.97		1.00		0.93		1.00
	[0.86-1.10]		[0.84-1.19]		[0.78-1.11]		[0.84-1.21]
3	1.02		1.17		0.88		0.84
	[0.89-1.16]		[0.97-1.40]		[0.72-1.07]		[0.68-1.03]
4	0.99		1.07		0.89		0.87
	[0.86-1.14]		[0.88-1.29]		[0.73-1.10]		[0.71-1.07]
5	1.04		1.12		0.94		**0.79***
	[0.90-1.21]		[0.92-1.38]		[0.76-1.17]		**[0.63-0.99]**
HB							
1	ref		ref		ref		ref
2	1.02		0.94		1.07		1.08
	[0.88-1.18]		[0.76-1.16]		[0.87-1.32]		[0.87-1.34]
3	1.01		0.90		1.02		1.08
	[0.88-1.17]		[0.74-1.09]		[0.82-1.27]		[0.87-1.36]
4	1.12		1.05		1.21		1.21
	[0.96-1.31]		[0.84-1.31]		[0.98-1.51]		[0.97-1.51]
5	1.06		1.03		1.11		1.24
	[0.89-1.26]		[0.80-1.31]		[0.87-1.42]		[0.96-1.59]
6	1.09		0.98		1.04		1.11
	[0.94-1.26]		[0.80-1.18]		[0.83-1.31]		[0.88-1.41]
7	1.07		0.96		1.20		0.88
	[0.84-1.35]		[0.67-1.38]		[0.88-1.64]		[0.64-1.22)

Statistically significant figure In bold. *P<0.05 **P<0.01 ***P<0.0001

7.4.2.2 Minor amputations

Overall, 1707 (59.3%) patients died in the follow up period following minor amputation, 56 (1.9%) within 30 days, 425 (14.8%) within 1 year and 1234 (42.9%) within 5 years. Of those who died, 64.6% (n=1102) had a diagnosis of diabetes. The median survival time was 77.1 months (71.1-81.6) (Table 7.6), 40.6 months longer than that seen following incident major amputation. Persons who went on to undergo a major amputation following the incident minor amputation had a significantly shorter survival time of 56.6 months (52.2-62.9) compared to those who did not (85.1 (79.4-90.0) months), p=<0.001) (Figure 7.5). Significant differences were seen by gender (Figure 7.6), age group (Figure 7.7), and when progression to major amputation was required after being stratified by age. Survival time for any age group was significantly shorter for those requiring a major amputation, apart from the group aged over 85 years. In this age group those who required a major amputation had a median survival time 3.9 months longer than those who did not progress to a major amputation.

Figure 7.8 shows the Kaplan-Meier survival curves for those patients who underwent minor amputation stratified by diabetes diagnosis. In the population without diabetes 605 (47.2%) people died over the follow up period, 24 (1.9%) in the first 30 days, 148 (11.6%) within 1 year and 424 (33.1%) at 5 years. In the population with diabetes 1102 (69%) people died over the period. People without diabetes had a median survival 64 months longer than those with diabetes (non-diabetes: 122.6 months [102.2-134.3]; diabetes:58.3 months [53.3-63.5]). There was no difference in mortality rate at 30 days between the two groups. Thirty-two (2%) people with diabetes died at 30 days. At 1-year post amputation 277 (17.4%) people with diabetes had died and by 5 years 50.8% (810) of the population with diabetes had died.

Table 7.6 Crude rates of cumulative percentage of persons undergoing minor lower extremity amputation that died at 30 day, 1 and 5 years

									Survival	[months]	
variable [n]	N	n died	30-days	%	1-year	%	5-year	%	Median	95% CI	P value
All [2877]		1707	56	1.9	425	14.8	1234	42.9	77.1	[71.1-81.6]	
Sex											
Men	1865	1160	39	2.1	304	16.3	845	45.3	69.7	[64.7-76.4]	**<0.001**
Women	1012	547	17	1.7	121	12.0	389	38.4	87.6	[81.2-98.5]	
Age											
<65	1102	418	12	1.1	66	6.0	255	23.1	145.9	[143.8-NA]	**<0.001**
65-74	748	451	6	0.8	92	12.3	310	41.4	80.6	[69.7-90.7]	
75-84	742	587	27	3.6	162	21.8	449	60.5	44.2	[38.9-48.7]	
85+	285	251	11	3.9	105	36.8	220	77.2	22.4	[17.1-26.0]	
Diabetes											
No	1281	605	24	1.9	148	11.6	424	33.1	122.6	[102.2-134.3]	**<0.001**
Yes	1596	1102	32	2.0	277	17.4	810	50.8	58.3	[53.3-63.5]	
Major											
no	2300	1283	47	2.0	331	14.4	935	40.7	85.1	[79.4-90.0]	**<0.001**
yes	577	424	9	1.6	94	16.3	299	51.8	56.6	[52.2-62.9]	
Age and further Amputation											
Minor only											**<0.001**
<65	870	284	10	1.1	49	5.6	174	20.0	na	na	
65-74	575	323	red	red	69	12.0	227	39.5	89.4	[79.2-102.3]	
75-84	615	466	23	3.7	121	19.7	350	56.9	47.9	[42.9-55.9]	
85+	240	210	11	4.6	92	38.3	184	76.7	21.4	[14.5-26.0]	
Major											
<65	232	134	red	red	17	7.3	81	34.9	89.7	[70.0-112.5]	
65-74	173	128	red	red	23	13.3	83	48.0	64.7	[52.2-75.7]	
75-84	127	121	red	red	41	32.3	99	78.0	30.3	[24.3-38.4]	
85+	45	41	red	red	13	28.9	36	80.0	25.0	[16.5-37.8]	

Major: Major amputation following minor amputation; red: Redacted to obtain anonymity as numbers less that 5.. p is log rank between categories for median survival time. Not calculated for diabetes status.

Figure 7.5 Crude Kaplan- Meier survival curves after incident minor amputation stratified by progression to major amputation

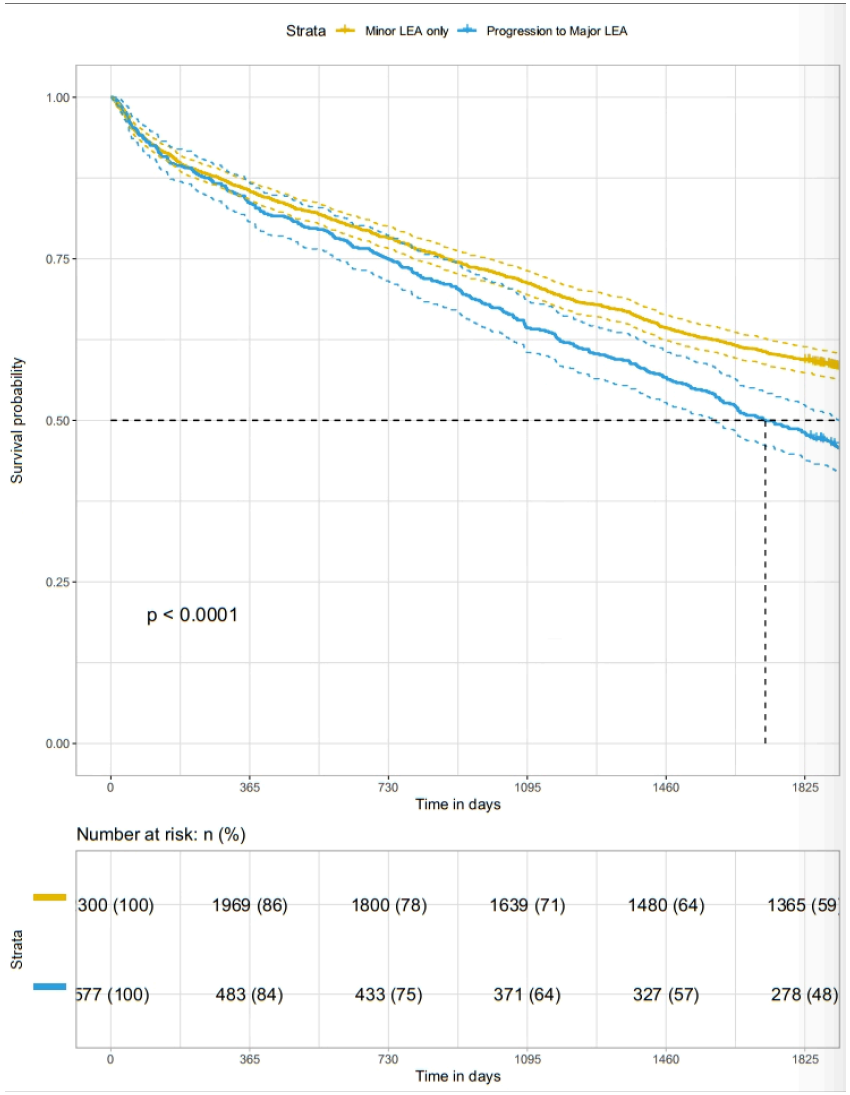


Figure 7.6 Crude Kaplan- Meier survival curves after incident minor amputation stratified by gender

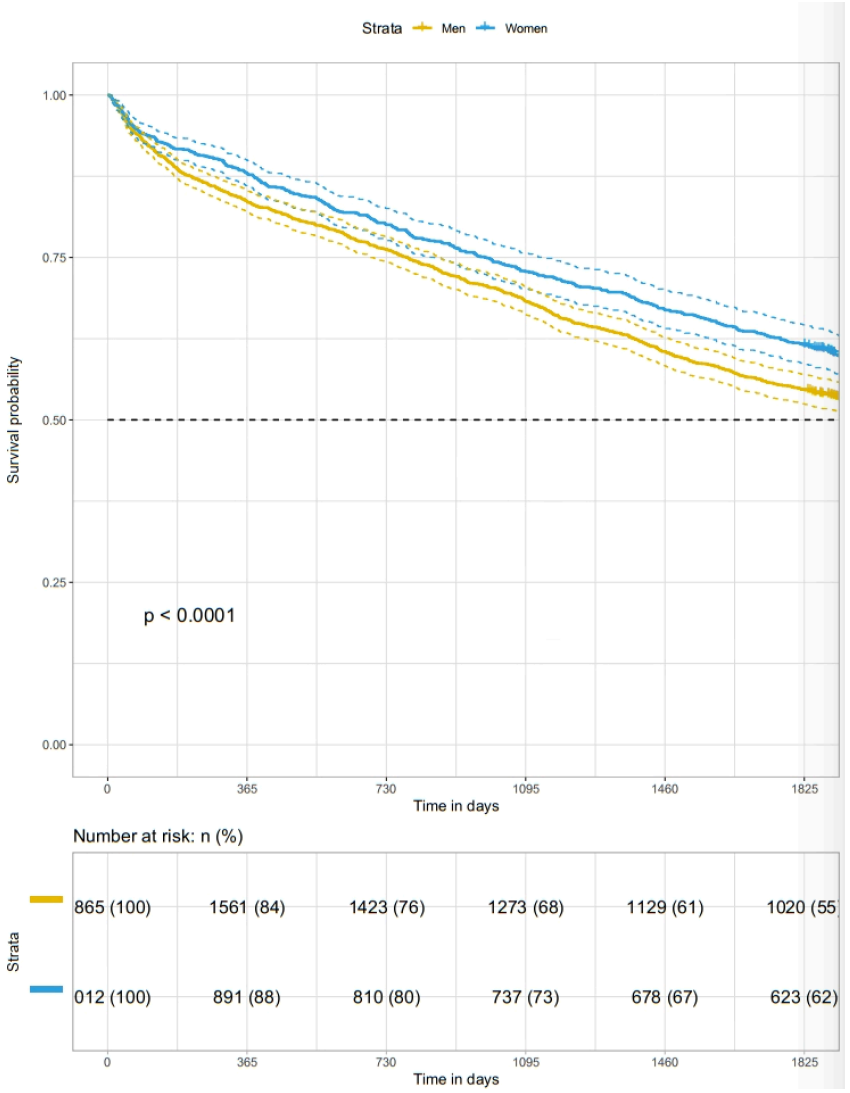


Figure 7.7 Crude Kaplan- Meier survival curves after incident minor amputation stratified by age categories

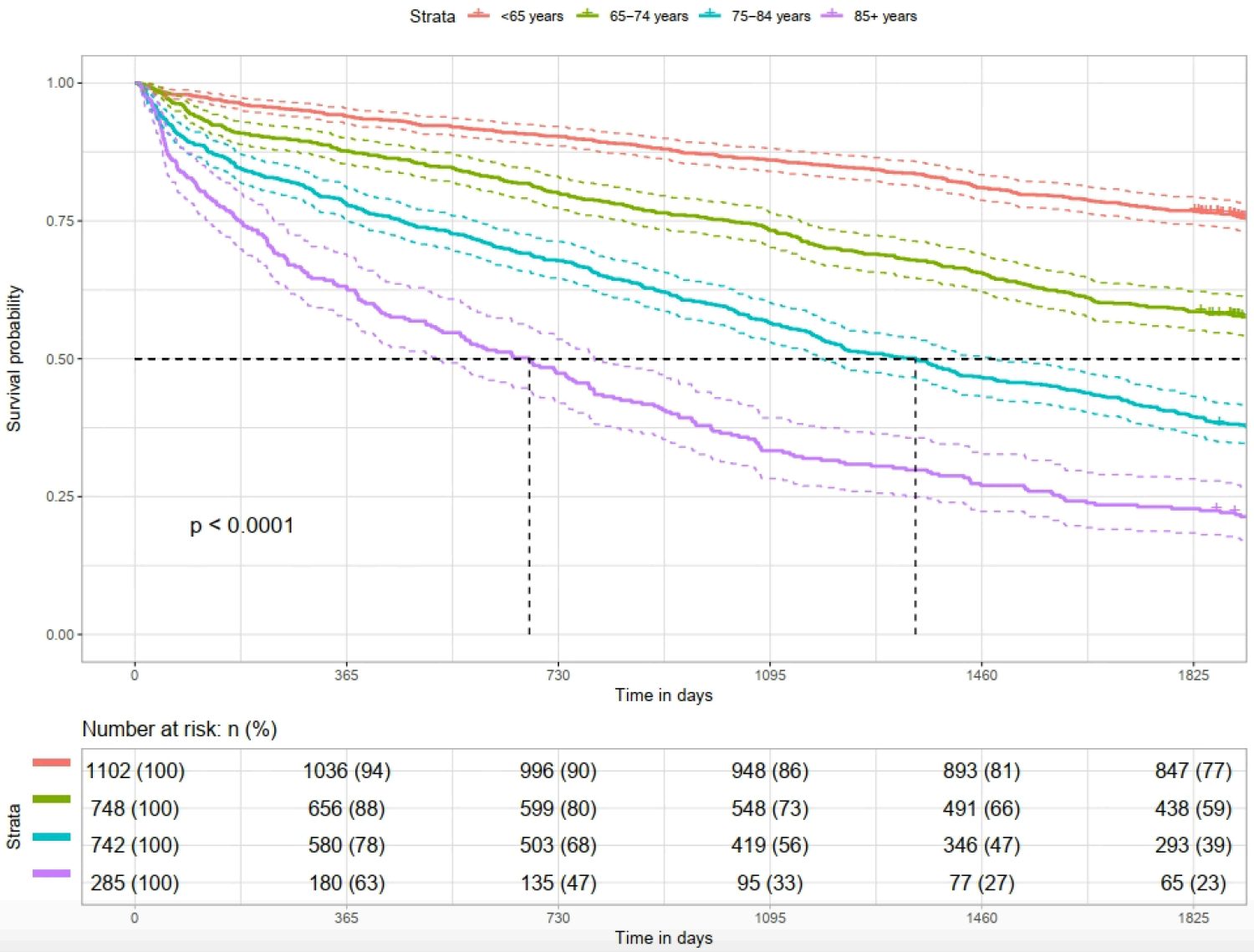
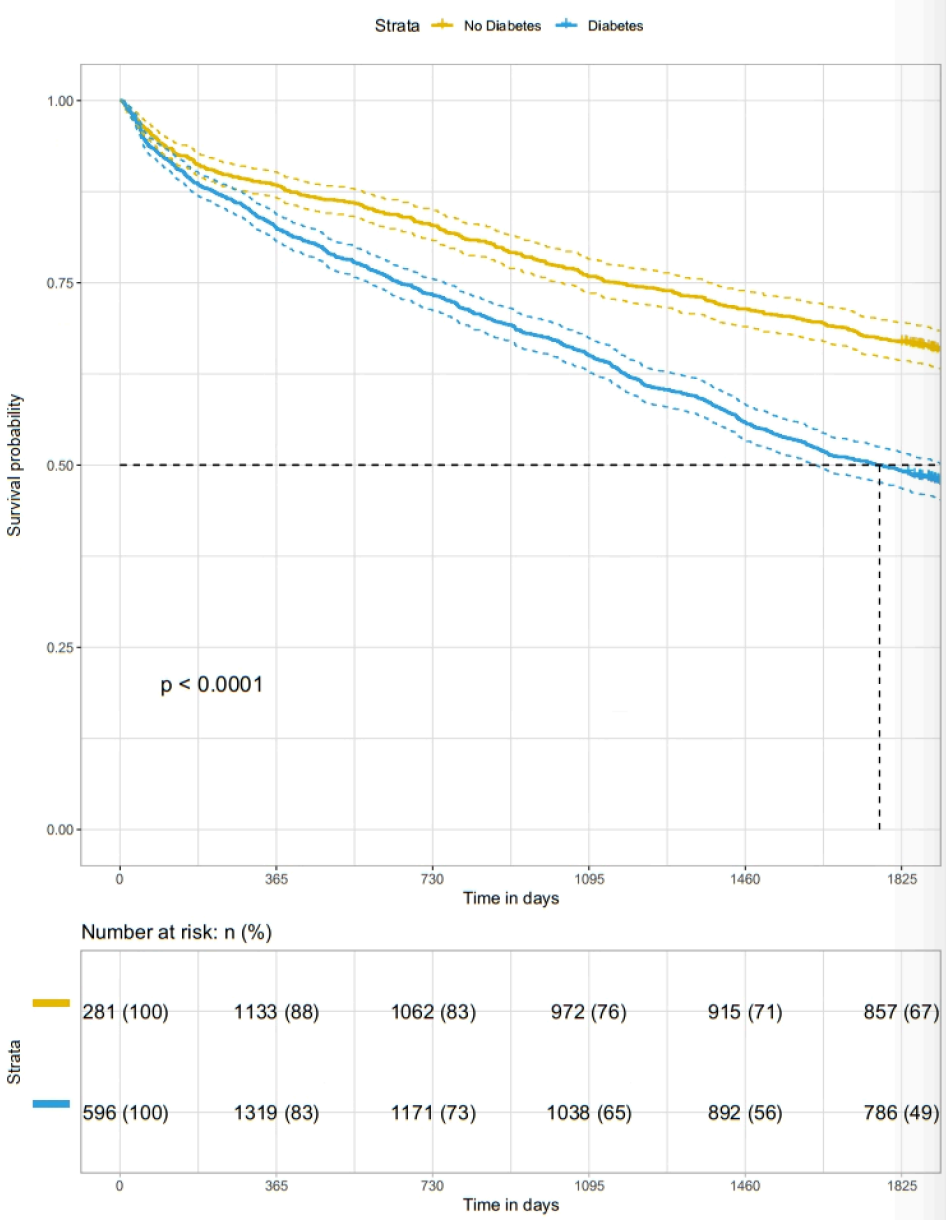


Figure 7.8 Crude Kaplan- Meir survival curves after incident minor amputation stratified for history of diabetes



The results of all Cox regression analysis models are shown in Table 7.7. In the unadjusted model, the relative mortality risk associated with diabetes was significant in all time periods excluding at 0 to 30 days and at 60 days to 6 months. The greatest risk of mortality associated with diabetes was at 6 to 12 months with a hazard ratio of 2.30 [1.56-3.39]. Increasing age, male gender, increasing Charlson index score, progression to a major amputation and all medical risk factors were associated with an increased risk of mortality. As with major amputation, a Charlson index score of 3 or more compared to a score of 0 inferred the

greatest risk of mortality, with a hazard ratio of 7.56 [4.80-11.9]. In the unadjusted model a history of a limb salvage procedures had a hazard ratio of 2.02 [1.82-2.23]. Increasing WIMD quintile was also associated a decreasing risk of mortality for all quintiles except quintile 4. There was some variance in risk between health boards with the HR of mortality for HB5 significantly higher than that of HB1.

The mortality risk associated with diabetes adjusted for age, sex and gender (Model 1) was 1.17 [0.70-1.19] at 0 to 30 days, 1.91 [1.19-3.07] at 31 to 60 days, 1.31 [0.95-1.80] at 61 days to 6 months, 2.46 [1.67-3.62] at 6 months to 1 year, 1.93 [1.45-2.56] at 1 to 2 years, 1.47 [1.12-1.93] at 2 to 3 years and 2.40 [1.92-3.00] at 3 to 5 years. Increasing age remained significantly associated with mortality, along with gender, such that women had a 28% lower risk for mortality compared to men; HR 0.72 [0.65-0.80]. Model 4, which included all variables, was taken as the fully adjusted model as it was the most parsimonious model. There was evidence that increasing WIMD quintile independently affected mortality when controlling for other variables and model concordance index was greatest at 0.76 $\sigma\bar{x}$ 0.006 predicting over 75% of mortality that occurred.

In this fully adjusted model diabetes was associated with an increased risk of mortality at 30-60 days (1.61 [1.00-2.59]), 6-12 months (1.97 [1.22-2.90]), 1-2years (1.59 [1.19-2.12]) and 3-5 years (1.98 [1.58-2.49]). Increasing age was significantly associated with an increased risk of mortality (HR 1.06 [1.05-1.06] per year), as was increasing Charlson index (score 1, 1.50 [1.33-1.69]; 2, 1.87 [1.53-2.29]; 3+ 2.30 [1.39-3.82]), a history of ESRD (1.98 [1.60-2.45]), MI (1.17 [1.01-2.45]), CCF (1.30 [1.12-1.50]) and PVD (1.65 [1.45-1.87]). There was no significant association with mortality associated with progression to major amputation, a history of a limb salvage procedure within the 2 years prior to amputation admission, a history of HTN or CVA. When controlling for other confounding factors, there was no significant variance in mortality risk for any health board.

Table 7.7 Result of cox regression model analysis of predictors for mortality after incident minor amputation

		Unadjusted	[95% CI]	Model 1	[95% CI]	Model 2	[95% CI]	Model 3	[95% CI]	Model 4	[95% CI]
Diabetes	0-30 days	1.09	[0.65-1.83]	1.17	[0.70-1.97]	1.14	[0.68-1.91]	0.97	[0.58-1.64]	0.99	[0.59-1.66]
	31-60 days	**1.78***	**[1.11-2.86]**	**1.91****	**[1.19-3.07]**	**1.87****	**[1.16-3.00]**	1.59	[0.99-2.56]	**1.61***	**[1.00-2.59]**
	61-6month	1.24	[0.90-1.70]	1.31	[0.95-1.80]	1.28	[0.93-1.76]	1.08	[0.78-1.48]	1.07	[0.78-1.48]
	6-12 month	**2.30*****	**[1.56-3.39]**	**2.46*****	**[1.67-3.62]**	**2.40*****	**[1.63-3.54]**	**2.01*****	**[1.36-2.96]**	**1.97*****	**[1.22-2.90]**
	1-2 Years	**1.78*****	**[1.34-2.36]**	**1.93*****	**[1.45-2.56]**	**1.90*****	**[1.43-2.52]**	**1.59****	**[1.20-2.12]**	**1.59****	**[1.19-2.12]**
	2-3 Years	**1.38***	**[1.05-1.80]**	**1.47****	**[1.12-1.93]**	**1.46****	**[1.11-1.91]**	1.22	[0.93-1.60]	1.21	[0.92-1.56]
	3-5 Years	**2.24*****	**[1.79-2.79]**	**2.40*****	**[1.92-3.00]**	**2.38*****	**[1.90-2.97]**	**2.00*****	**[1.59-12.50]**	**1.98*****	**[1.58-2.49]**
Age		**1.05*****	**[1.05-1.06]**	**1.06*****	**[1.05-1.06]**	**1.05*****	**[1.05-1.06]**	**1.05*****	**[1.05-1.06]**	**1.06*****	**[1.05-1.06]**
Women		**0.79*****	**[0.72-0.88]**	**0.72*****	**[0.65-0.80]**	**0.79****	**[0.71-0.88]**	**0.86****	**[0.75-0.93]**	**0.80*****	**[0.72-0.90]**
Charlson	1	**1.99*****	**[1.79-2.22]**			**1.74*****	**[1.56-1.94]**	**1.50*****	**[1.33-1.68]**	**1.50*****	**[1.33-1.69]**
index	2	**3.67*****	**[3.11-4.34]**			**2.54*****	**[2.15-3.01]**	**1.85*****	**[1.52-2.26]**	**1.87*****	**[1.53-2.29]**
	3+	**7.56*****	**[4.80-11.9]**			**5.21******	**[3.30-8.24]**	**2.16*****	**[3.31-3.58]**	**2.30****	**[1.39-3.82]**
Major		**1.46*****	**[1.31-1.63]**			**1.16***	**[1.03-1.30]**	1.06	[0.95-1.19]	1.02	[0.91-1.15]
Limb salvage		**2.02*****	**[1.82-2.23]**			**1.37*****	**[1.23-1.52]**	1.11	[0.99-1.24]	1.10	[0.98-1.24]
HTN		**1.99*****	**[1.79-2.20]**					1.08	[0.97-1.21]	1.07	[0.96-1.20]
ESRD		**2.34*****	**[1.92-2.85]**					**2.03*****	**[1.64-2.50]**	**1.98*****	**[1.60-2.45]**
MI		**2.31*****	**[2.01-2.64]**					**1.18***	**[1.01-1.36]**	**1.17***	**[1.01-1.36]**
CVA		**2.07*****	**[1.78-2.40]**					1.15	[0.98-1.36]	1.15	[0.97-1.35]
CCF		**3.22*****	**[2.87-3.62]**					**1.34***	**[1.16-1.55]**	**1.30*****	**[1.12-1.50]**
PVD		**2.50*****	**[2.25-2.78]**					**1.62*****	**[1.42-1.84]**	**1.65*****	**[1.45-1.87]**
WIMD	2	**0.86***	**[0.75-0.99]**							0.94	[0.82-1.08]
	3	**0.78*****	**[0.68-0.90]**							**0.73*****	**[0.63-0.84]**
	4	0.88	[0.76-1.02]							**0.80****	**[0.69-0.94]**
	5	**0.74*****	**[0.63-0.86]**							**0.71*****	**[0.60-0.84]**
Health Board	2	1.01	[0.87-1.18]							1.05	[0.89-1.23]
	3	1.11	[0.96-1.29]							1.09	[0.93-1.26]
	4	1.06	[0.90-1.26]							1.17	[0.99-1.40]
	5	**1.23***	**[1.03-1.47]**							1.13	[0.94-1.37]
	6	1.17	[0.98-1.39]							1.11	[0.93-1.33]
	7	1.19	[0.95-1.50]							1.04	[0.81-1.32]

Statistically significant figure In bold. *P<0.05 **P<0.01 ***P<0.0001

7.4.3 Cause of Death

For the population with diabetes the leading cause of death as reported following major amputation was coronary heart disease (n=269, 26.5%) (Table 7.8). The second leading cause of death for the population was recorded as 'diabetes mellitus' (n=189, 18.6%) and the third cause was 'other circulatory causes', recorded for 10% (n=102) of patients. For this population the main disease within the 'other circulatory causes' category was PVD (n=33) recorded for 32.4% of the deaths.

For the population without diabetes the leading cause of death following major amputation was other circulatory causes (n=236, 25.7%). The majority of these deaths were attributed to PVD, recorded as the underlying cause in 175 cases, 74.2% of the deaths in the other circulatory cause category and 19% of all deaths. PVD was recorded for more deaths than the secondary leading cause of death, coronary heart disease, resulting in 131 deaths (14.3%).

As was the case for major amputation, for the population with diabetes the leading cause of death following minor amputation was coronary heart disease resulting in 318 deaths (28.9%). The second leading cause of death was again diabetes mellitus 167 (n=15.2%) and the third other circulatory causes. The main disease recorded within the other circulatory causes category was heart failure (n=21, 21.2%) followed by PVD (n=16, 16.2%).

In the non-diabetes population, there was less variance in the frequency of death causes than for the diabetes population or for major amputation. The leading recorded cause was again other circulatory causes, noted as the underlying cause of death in 14.9% of cases (n=90). This was closely followed by coronary heart disease in 12.7% of cases (n=77). The leading underlying diagnosis within the other circulatory causes category was PVD in 43.3% of cases (n=39).

Table 7.8 Underlying cause of death stratified by population and amputation type

Underlying cause of death	Major Amputation				Minor Amputation			
	Diabetes		Non-diabetes		Diabetes		Non-diabetes	
	Number	%	Number	%	Number	%	Number	%
Accidents	4	0.4	5	0.5	13	1.2	6	1.0
Bowel Cancer	12	1.2	11	1.2	15	1.4	13	2.1
Cerebrovascular	58	5.7	64	7.0	62	5.6	49	8.1
Chronic Lower Respiratory Disease	31	3.1	64	7.0	22	2.0	44	7.3
Cirrhosis and other diseases of the liver	11	1.1	5	0.5	18	1.6	5	0.8
Coronary Heart Disease	**269**	**26.5**	131	14.3	**318**	**28.9**	77	12.7
Dementia and Alzheimer's disease	29	2.9	28	3.0	28	2.5	33	5.5
Diabetes mellitus	189	18.6	9	1.0	167	15.2	3	0.5
Digestive excluding cirrhosis	37	3.6	46	5.0	45	4.1	20	3.3
Drug related	1	0.1	5	0.5	0	0.0	4	0.7
Flu and Pneumonia	79	7.8	63	6.9	78	7.1	60	9.9
Genitourinary	35	3.4	21	2.3	39	3.5	24	4.0
Ill-defined	4	0.4	7	0.8	1	0.1	9	1.5
Infectious diseases	23	2.3	23	2.5	22	2.0	12	2.0
Lung Cancer	20	2.0	37	4.0	16	1.5	35	5.8
Nervous system diseases exc Alzheimer's disease	3	0.3	15	1.6	10	0.9	8	1.3
Other	0	0.0	2	0.2	2	0.2	2	0.3
Other Cancer	50	4.9	73	7.9	63	5.7	54	8.9
Other Circulatory	102	10.0	**236**	**25.7**	99	9.0	**90**	**14.9**
Other External	7	0.7	8	0.9	5	0.5	3	0.5
Other Respiratory	19	1.9	25	2.7	31	2.8	14	2.3
Prostate Cancer	5	0.5	10	1.1	6	0.5	11	1.8
Residual	27	2.7	31	3.4	40	3.6	28	4.6
Suicide	0	0.0	0	0.0	2	0.2	1	0.2

exc: excluding; Highest frequency underlying cause for each category in bold

7.5 Discussion

This population-based study examined mortality following incident amputation in the Welsh population between 2006-2013 with a minimum 5-year follow-up period. The analysis was stratified by amputation level with the main focus to examine the effect of diabetes as a predictor of mortality. This is the first study investigating mortality following incident amputation secondary to diabetes within the Welsh population.

As expected, the mortality following major amputation was high. The mortality rate was 61.9% at 5 years in the total population and 67% in the population with diabetes. Direct comparison of mortality rates following amputation can be difficult due to differences in population, amputations definition and reporting. However the findings were congruent with a recent global systematic review of mortality following amputation (Thorud et al., 2016) where an estimated 5-year mortality rate post major amputation of between 52% and 80% was reported in people with diabetes.

A mortality rate of 9.2% at 30 days highlights the frailty of the study population. This finding was comparable with an estimated mortality rate of 10% presented in studies from other western populations (Davenport, Ritchie, & Xenos, 2012; Icks et al., 2011; Eszter Panna Vamos et al., 2010b) and lower than that seen in Scandinavian studies with a reported rate of between 19-30% (Eskelinen et al., 2004; Fortington et al., 2013; Kristensen, Holm, Kirketerp-Møller, Krasheninnikoff, & Gebuhr, 2012). Differences in health service provision and clinical decision making may explain some of this variation. It is suggested that in Scandinavian populations major amputation is utilised more frequently within a palliative setting for pain relief in critical limb ischaemia than within the UK(Thorud et al., 2016). In this study, within the cohort of patients undergoing minor amputation the time to death in those progressing to a major lower extremity amputation over 85 years of age was longer than for those with did not. This is suggestive that within this study population the frailest patients did not undergo major amputation.

As expected, the mortality rate for the population undergoing incident minor amputation was lower at all time periods than for the population undergoing incident major amputation. The median survival following incident minor amputation was over 3 years longer than that in the

incident major amputation analysis and the 5-year mortality rate was 42.9%, almost 20% lower. There are few studies within the literature at present reporting mortality following minor amputation for populations with or without diabetes of which to compare. The findings are in keeping with the studies that have stratified by amputation level. Yammine et al (Yammine, Hayek, & Assi, 2020) reported a 5-year mortality rate of 44.1% in a meta-analysis of minor amputations performed in patients with PVD or diabetes and in the global systematic review performed by Thorud et al the estimated 5-year mortality rate was In the range of 29-69% (Thorud et al., 2016). Major amputation is viewed as an adverse outcome of diabetes, the result of the end stages of a disease process, whereas minor amputations are viewed as a treatment; a procedure to remove infection and necrosis with the aim encouraging wound healing (PHE, 2019). With this view of the procedures in mind, mortality is expected to be lower in the incident minor amputation cohort as it is expected that the patients will recover from the procedure and prevent the requirement for major amputation. Twenty percent of the people within the minor cohort did progress to require a major amputation over the study period and as expected, for those patient's survival time was significantly shorter. However, even in patients who did not go on to require major amputation the mortality was considerable and as such, minor amputation should be viewed as a significant event in a person's disease course.

The main dependant variable of interest within the study was the effect of diabetes status on mortality risk over time. When controlling for other variables in the first time period after incident major amputation, mortality was lower in the population with diabetes compared to those without. Subsequently, this risk reversed and at 6 months so that the mortality risk for people with diabetes was significantly increased compared to those without. The influence of diabetes on survival after major amputation has previously been described as time dependent, with diabetes showing a similar (Aulivola et al., 2004; Mayfield et al., 2001; Subramaniam, Pomposelli, Talmor, & Park, 2005) or reduced risk (Icks et al., 2011; Pohjolainen & Alaranta, 1998) of mortality in the short-term but an increased risk of mortality in the long-term. It has been postulated that the initial decrease in mortality risk is due to a greater frequency of monitoring by multiple specialists over the initial period. As demonstrated in this study, the population with diabetes often have a greater number of co-morbid conditions (Icks et al., 2011). However, it would be expected that as the population

with diabetes have a greater number of co-morbidities, they would be frailer at the time of procedure and the burden of the operation would be greater, increasing the risk of post-operative mortality (Amrock & Deiner, 2014). This is then suggestive that the decreased risk of mortality in the initial time period is in relation to the care provided rather than due to patient characteristics. If this were the case it would be expected that this trend would be reflected following incident minor amputation. In this study this was not observed, however, the mortality rate within the first year following minor amputation was minimal and it may be that the effect size was too small to be observed with the sample size studied.

It Is unclear what drives the initial decreased risk in mortality for patients with diabetes undergoing major amputation and findings within the literature are conflicting. People with diabetes were more likely to undergo BKA due to the pattern of vascular involvement in PVD with diabetes (American Diabetes Association, 2003). Patients who undergo BKA are often younger, as was found in this study, and have been shown to have a longer survival than those undergoing AKA (Subramaniam et al., 2005) which could explain some of the short term variance in survival for the population with diabetes in the unadjusted model. However, this variance held true after adjusting for amputation level.

When the analysis of major amputation was stratified for level, the effect of diabetes on the risk of death was only significant for BKA. For those patients undergoing AKA there was no significant difference in mortality risk associated with diabetes during any follow-up period. These findings suggest that these procedures occur in the most unwell patients in both populations, mitigating the effect of diabetes. The amputations are often performed in patients who are the most morbid and are less likely to mobilise postoperatively with a prosthesis (H. G. Smith, 1950) in both populations with and without diabetes. The highest level of amputation is chosen as the priority for the procedure is post-operative wound healing reducing the risk of further procedure. When the results were stratified by age and amputation level, survival time was considerably shorter for all age categories in both populations with and without diabetes undergoing AKA, again suggesting that these individuals are more unwell at the time of procedure.

For both major and minor amputation, diabetes was associated with an increased risk of mortality in the five years following amputation. This finding is concerning as diabetes is the leading cause of non-traumatic amputation within the UK. There is some disagreement within the literature regarding mortality within the population with diabetes. A number of studies examining mortality following major amputation reported no associated increased risk of death with a history of diabetes (Thorud et al., 2016). The majority of these studies were not stratified by time and were not population based. Icks et al, reported findings similar to those discussed in this chapter (Icks et al., 2011) in their time-stratified study of the German population between 2004-2007. The trend was again reflected in the findings of Subaramaniam et al (Subramaniam et al., 2005) in an American population. Other authors found no association with diabetes and mortality in time-stratified analysis, but the methods used for assessing time-trend varied. Fortington et al (Fortington et al., 2013) used logistic regression to compare the characteristics of those who died with those who did not at different time points rather than utilising a time dependent analysis. This may explain some of the variance in findings, along with variance in study populations and definitions of amputation.

For both major and minor amputation, a history of PVD increased the risk of post-operative mortality. For those undergoing incident major amputation, 80% of patients had a history of PVD and for incident minor amputation 58.7% had a history of PVD. Despite this, only 34% of the total major amputation population and 25.7% of the minor amputation population had undergone a limb salvage procedure in the two years prior to amputation. The percentage of patients undergoing a limb salvage procedure compared to the number of patients with PVD was lower in the population with diabetes than in those without for both the major and minor amputation analysis. Forty one percent of people with diabetes and PVD underwent a limb salvage procedure compared to 44% in the non-diabetes group in the incident major amputation population. For the incident minor amputation population 41% of people with diabetes and PVD underwent a limb salvage procedure compared to 50% in the non-diabetes group. For major amputation a history of limb salvage procedure reduced the risk of mortality by 15% when controlling for other factors. Considering this and NICE guidance (NICE, 2018) that recommends attempting limb salvage procedures prior to amputation for PVD, the number of procedures performed seems low. It may be that a large number of patients were

admitted with critical limb ischaemia without revascularisation option. This was not evaluated within this study. People with diabetes are more likely to have asymptomatic PVD (Thiruvoipati et al., 2015) and thresholds for limb salvage procedures may not be met as readily as the diagnosis is often dependent on rest pain (NICE, 2018). This may explain the lower number of procedures in the population with diabetes. However, with limb salvage procedures the only modifiable risk factor within the analysis to infer a survival benefit, this could be an area for further research within this population along with other aspects of preoperative and preventative care.

7.6 Strengths and limitations

The main strength of the study was that it was a population analysis; not only had this population not been investigated before, it is one of the few studies of amputation mortality that has examined an entire population. The long study period, with a minimum of 5-year follow-up for all persons allowed a large sample size to be maintained to the end analysis point of 5-year mortality. As the data were analysed in SAIL, it was also possible to assess cause of death from the national ADDE, which had not previously been reviewed in other studies.

Several limitations have to be considered. As with any analysis using hospital data, the findings are only as reliable as the coding. Although smoking status was available for some patients through hospital data, this coding has been shown to be unreliable. For a subset of patients, it was possible to assess smoking status more reliably using GP records but as there is not full GP coverage for the entire Welsh population within SAIL, these data could not be used in the entire population analysis. This was also true of other clinical variables such as HbA1c, cholesterol or a history of ulceration prior to amputation. These variables would have helped to further assess disease severity and may have increased the predictive value of the cox regression models. As with any retrospective analysis there were some missing data but this proportion was small.

It was not possible to determine laterality of the amputations and it is possible when minor preceded major amputation the operations may have been on separate limbs. As many of the risk factors for amputation are systemic and a 5-year look back period for incident amputation was used. it is unlikely that discriminating limb of operation would have an effect on the outcomes seen but one cannot be certain.

CHAPTER 8

General Discussion

8.1 Aims of thesis

The overarching aim of this thesis was to understand the burden of diabetes-related amputation and the associated risk factors within Wales at the current time and over its recent history. The thesis investigated amputation rates and mortality in the Welsh population with and without diabetes over the last decade for both major and minor amputations. The thesis also examined risk factors for diabetes related amputation at a person, health board, population level using different methodologies to quantify specific risks. This included a RCA to assess differences in care provision and questionnaires to understand patient's knowledge and protective behaviours.

8.2 Root cause analysis and system related risk factors

It is estimated that 80% of amputations secondary to diabetes are preventable (NICE, 2016). The most important finding from the root cause analysis was that almost all of the amputations in the study period were determined potentially or definitely preventable. A RCA of diabetes related major amputations undertaken in Shielfield, which had the highest amputation rates within England in 2002, concluded that 20% of amputations were potentially preventable (Diabetes UK, 2015b). However, this analysis did not include any information relating to the patient's journey in primary care; of note a large number of the delays identified within our local RCA where prior to secondary care admission. Further studies of the impact following intervention from previous RCA such as the introduction of MDT and streamlined care pathways have demonstrated a 50% and 60% reduction in amputation rates (Krishnan et al., 2008; R. B Paisey et al., 2018b). For Sheffield, major amputation rates fell by over 50% once interventions were established (Diabetes UK, 2015b). This suggests that a greater number of the amputations reviewed in their initial RCA were likely preventable, in keeping with our findings. More importantly, this finding supports the concept that a change of service provision could potentially result in a reduction in amputations within ABMU. The observations from this RCA identified a number of areas in which resources could be directed, which may reduce the rate of amputation within ABMU and many of the root causes in the review related to an acceptance within the clinical environment that amputation was inevitable. The literature from other studies demonstrates

this is not the case, as discussed previously the effect of implementing the results of a RCA in other regions has been found to produce a measurable amputation reduction. Education relating to this for patients and within the clinical environment is required. Within our review, long delays were noted in the pathway between primary and secondary care and streamlining of services between care levels may help with this, along with formation of a formal MDT and patient education. Unfortunately assessing the outcome of these measure could take several years, since as discussed previously, amputation is the end stage of a long disease process. To assess any variance, it is important to accurately classify the amputation rate within the population at present. This was addressed later in the thesis.

As expected, the greatest contributory factors were patients' clinical condition at time of presentation. In many cases root causes were found to be disease related which was to be expected as amputation occurs as the end event of a long disease process. Patient outcomes were likely affected by the disease length and patient adherence to treatment in addition to the treatment received in primary and secondary care prior to and at the time of referral. Management prior to the amputation admission could have prevented the severity at presentation in many of the cases and poor patient engagement with services played a role in a considerable number of cases. Studies have demonstrated that patients with diabetes related foot disease have a low self-awareness of what is required for foot health and a low internal health locus of control. Ultimately a poor understating that their actions will benefit their health outcomes (E. McBride, 2016). Although the evidence on utilizing education as a preventative strategy for diabetes-related foot disease is inconclusive it does form the cornerstone of NICE preventative guidelines (Dorresteijn et al., 2014; Mason et al., 1999; Morey-Vargas & Smith, 2015). As such, these outcomes may have been changed with better interpersonal relationships, health education and trust of the service and the effect of communication was determined to be an influencing factor in 31 cases.

8.3 Social and clinical risk factors

Along with risk factors related to variance in care, this thesis explored other socio-economic risk factors such as socio-economic deprivation, smoking status and BMI. The findings within

the current literature examining the association between social deprivation and amputation risk within the diabetes population are inconclusive, with some studies reporting a positive correlation (Amin et al., 2014; Shan M Bergin, Brand, Colman, & Campbell, 2011b; Hippisley-Cox & Coupland, 2015b), some reporting a complicated association (Leese et al., 2013), and some reporting no correlation of note (Naseer Ahmad et al., 2014). There was no statistically significant relationship with amputation noted in the current study but there was a trend towards a reduction in social depravation and a reduced chance of amputation; this was greatest between the most deprived to the least deprived quintile with an OR of amputation of 0.55 [0.28-1.05]. The trend towards a decreased risk may be related to a number of factors such as self-care, education, occupational risk or nutrition which require further exploration. This finding was in keeping with other population-based studies and a study in a secondary care population in England (Shan M Bergin et al., 2011b; Gurney et al., 2018; Leese et al., 2013). The association between ulceration and deprivation has been demonstrated more conclusively in the literature, and it may be as in other studies that the analysis was underpowered and further investigation is required within a larger population.

When stratified into categories being underweight was associated with a trend towards an increased risk of amputation (OR 2.50 [0.07-84.95], p=0.07). This 'obesity paradox' has been demonstrated previously (Biasucci et al., 2010; M.-W. Sohn et al., 2012) and although not yet fully understood(M. W. Sohn, Budiman-Mak, Lee, Oh, & Stuck, 2011) it is likely to represent an indicator of frailty in those undergoing amputation. This was reflected the findings for cholesterol with an inverse association between increasing cholesterol and amputation. This trend was also seen when looking at foot risk in a previous paper on this secondary care population with those in the high-risk foot risk category having significantly lower cholesterol compared to those in the low foot risk category (4.1mmol/L:4.3mmol/L, high risk:low risk, p=0.03) (R Thomas et al., 2010a). This may be due to malnutrition associated with disease severity (Zhang et al., 2013).

The lack of association with smoking status was an interesting finding as there is substantial evidence indicating smoking is a risk factor for CVD (Daar et al., 2007) and hypertension (A

Virdis, Giannarelli, Fritsch Neves, Taddei, & Ghiadoni, 2010) and smoking is a major risk factor for peripheral vascular disease in the diabetes and non-diabetes population(Thiruvoipati et al., 2015). Theoretically there are a number of reasons why smoking would increase the risk of amputation, with detrimental effects on would healing, its association with PVD, CHD, stoke and neuropathy (Solomon Tesfaye et al., 2005). Despite this the evidence for its effect on the risk of amputation in persons with diabetes is contradictory and scarce. Most studies that do explore the relationship between smoking and amputation risk in diabetes are small cohort studies and do not control for other variables. A recent meta-analysis reported that smoking increased the risk of amputation, however this publication contained mainly small cohort studies and again could not control for other variables (M. Liu et al., 2018). The findings of this chapter did contradict the findings of the meta-analysis and it may be that the sample size was too small, as the odds were headed towards an increase risk. This requires investigation with a larger study but as discussed previously in the thesis, smoking is coded poorly in routine health data.

8.4 Patient education

The central aim of chapter 5 was to examine the association between knowledge and behaviour in a sample of persons with diabetes. Foot care knowledge was significantly positively correlated with behavioural score even after controlling for gender, history of foot problems and diabetes care provider. This association was in keeping with the findings of other similar studies in a number of other countries (Indrayana et al., 2019; Rajan et al., 2007; Shrestha, Aacharya, Shrestha, & Madhav, 2017). There is limited literature examining knowledge and practice of foot care in a similar population to this one, however, most of the studies exploring knowledge and foot care behaviours found a positive association between improving foot care knowledge and self-reported behaviour at least in the short term.

In the study population a high-risk foot or a history of diabetes-related foot disease was significantly associated with higher knowledge and behaviour score. In a larger American study of 728 patients, amputation was strongly positively associated with foot care behaviour after controlling for age, race, knowledge and history of neuropathy (Olson et al., 2009). It

has been demonstrated previously that those patients with low-risk feet are unlikely to receive any information relating to foot complications and how to avoid them (Litzelman et al., 1993; McInnes et al., 2011). Although evidence is inconclusive as to whether education reduces the risk of ulceration, education has been shown to improve foot care knowledge and protective self-reported self-care behaviour in the short term (Dorresteijn et al., 2014). Excluding low-risk patients potentially excludes a group from an easily implemented risk reduction strategy.

Other areas identified in which simple interventions could be beneficial included encouraging foot checks. Less that 43% of participants were aware of the necessity to check shoes before wearing, or the need to check feet regularly. Although higher than that found within a study in an English population (Pollock et al., 2004), the finding is still of concern as these are simple measures that can reduce the risk of amputation. Only 184 of 378 (49%) of participants reported checking their feet once a day or more, again indicating a relationship between knowledge and behaviour and highlighting a neglected simple protective behaviour. However, the relationship between protective behaviour and amputation risk is not straightforward. In this study men performed significantly more foot care protective behaviours, but we know from epidemiological studies, that men have a significantly greater risk of diabetes foot disease (PHE, 2019). Quality data is not available exploring the relationship between footcare behaviour and amputation reduction and further research into this area is required (Goodall et al., 2020).

There was no significant association between general diabetes knowledge and foot care behaviour, only specific foot care knowledge. This was in keeping with a recent meta-analysis looking at health literacy where no association was found between general health literacy and foot self-care (Chen et al., 2018). It indicates that specific foot care education is required for protective behaviours. Despite this, it is possible that general diabetes knowledge is associated with amputation through a route other than behaviour, as poor glycaemic control is associated with amputation (E J Boyko et al., 1999) and low Michigan DKT scores are associated with poor glycaemic control (Al-Qazaz et al., 2011; Panja et al., 2005).

The amount of patients aware of their own foot risk in this cohort was well below the expected NICE standards, as knowledge of foot risk is one the key outcomes of an annual foot review (NICE, 2016). Less than half the participants reported knowing their own foot risk (41.2%). It was not possible to determine whether foot risk was not being assessed within the annual review, if participants were not being informed of their foot risk or whether the information was not being retained. If participants were not being informed or the assessment was not being performed this would put participants at risk of not receiving education, as risk stratification has been shown to influence the protective care given (Litzelman et al., 1993), and if patients cannot advocate for their own care they are less likely to be engaged with preventative care (Hilliard et al., 2015). This finding was reflected in the fact that patients in this study who had previous foot ulceration were more likely to report they had had foot care education as their risk was clear to practitioner and patient. This again highlighting an area for improvement that could be easily implemented. Over 20% of patients reported being dissatisfied with the education provided at present. If there could be a change in practice this should affect behaviour and ultimately diabetes-related foot disease prevalence and outcomes over time.

8.5 Incidence of amputation in Wales

In order to assess the effects of any preventative care it is important first to understand the current burden of disease. It was important to explore the whole population of Wales because there has been an association demonstrated between overall amputation rates and rates within the population with diabetes. In all populations the crude number of major amputations fell across the period and the minor amputation rates increased although not as prominently in the population without diabetes. As expected directly standardised amputation rates in the population with diabetes were considerably higher compared to those in the population without diabetes. This was apparent across all amputation types and for incident and total amputations with particularly high standardised rates for minor amputations in men when compared to the non-diabetes population. When adjusted for age and sex the incidence of incident major amputations in the male diabetes and non-diabetes population and in the female diabetes population decreased significantly over the period.

Despite the population with diabetes representing only 7% of the total population, over 50% of the incident amputations performed over the period were on persons with diabetes. The relative risk of major amputation in the diabetic population was high at 8.0 [7.9-8.1] over the period. This was in keeping with findings within England where the relative risk of amputation in the population with has been reported as ranging between 7.4 and 41.3. The variation can be explained by differences in study design and definitions used, making comparison difficult. Despite this, rates of amputation are still considerably larger within the diabetic population and with the consensus that most major amputations in patients with diabetes are preventable, the slow decline in incident amputation rate in this population is concerning.

However, rates of all major amputation in the total population with diabetes were lower than that found in England. For the whole of Wales for the rolling period of 2016-2018 in the population with diabetes we found a total major amputation DSR of 6.7 [6.0-7.5]/ 10 000 PY. In England for the period of 2015/16 to 2017/18 the DSR rate was 8.2/ 10 000 PY. There were no significant drop in amputation rates in England over a 6-year period between 2012 and 2018. The reduction in age and sex standardised major amputation rate in the male and female population with diabetes could be seen as a positive indicator of improvement in services within Wales. It is suggestive that national campaigns such as the introduction of markers in QOF, annual audits and campaigns such as 'Putting Feet First' are having an effect in Wales. Directly standardised rates of total minor amputation were found to have increased significantly in England between the period of 2012/13-2014/15 and 2015/16-2017/18 from 20.4/10 000 PY to 21.4/0,000 PY (PHE, 2019). This was not reflected in the Welsh population with no significant change in total or incident amputations over the period and considerably lower total DSR rates of 15.8/10 000 PY [14.6-17.1] in 2013-15 and 15.9/10 000 PY [14.7-17.2] in the 2016-2018 period. Although the rates of both major and minor amputation rates are lower in the Welsh population in this study, the minor-major ratios are similar to the PHE analysis. Major amputation is viewed as an adverse outcome of diabetes, the result of the end stages of a disease process, whereas minor amputations are viewed as a treatment; a procedure to remove infection and necrosis with the aim encouraging wound healing (PHE, 2019). With this view of amputations in mind major-minor ratio has been suggested for use as a care quality indicator. Major-minor ratio did not increase significant in the whole

population analysis over the study period but the HBs with the lowest amputation rate did demonstrate the highest major-minor amputation ratios for both populations.

We also identified that the amputation rates for both diabetes and non-diabetes populations varied significantly between HBs. There was clear heterogeneity across the HBs within Wales with incident and total amputation rates varying by up to 80 and 100% respectively. This was true across all amputation types, populations and over time. As predicted the HB with the highest amputation rate in the diabetes population also had the highest amputation rate in the non-diabetes population for all amputation types and over time suggesting that there could be differences within systems affecting all populations. These findings were suggestive that there are differences in the extent and prevalence of driving factors for amputation within each area. Further investigation is required to explore disparities in rates of change between the genders, HBs and if an increased rate of minor amputation reduces rates of major amputation when controlling for factors that may confound the association.

8.6 Mortality following amputation in Wales

Mortality following diabetes related amputation is as high as many common cancers. Variance in mortality has been demonstrated between and within countries due to variance in health care systems. This was the first study to explore mortality following incident amputation in Wales. As expected, the mortality following major amputation was high. The mortality rate was 61.9% at 5 years in the total population and 67% in the population with diabetes. The reported rates were congruent with a recent global systematic review of mortality following amputation (Thorud et al., 2016) where an estimated 5 year mortality rate post major amputation of between 52% and 80% was reported in people with diabetes.

There was a mortality rate of 9.2% at 30 days highlight the frailty of the study population. This finding was comparable with an estimated mortality rate of 10% presented in studies from other western populations (Davenport et al., 2012; Icks et al., 2011; Eszter Panna Vamos et al., 2010b). There was variance in mortality rates by amputation type, with those undergoing

major amputation having a significantly shorter life expectancy than those undergoing minor amputations in both the diabetes and non-diabetes population. The median survival following incident minor amputation was over 3 years longer than that in the incident major amputation analysis and the 5-year mortality rate was 42.9%, almost 20% lower. The findings are in keeping with the studies that have stratified by amputation level. Yammine et al (Yammine et al., 2020) reported a 5-year mortality rate of 44.1% in a meta-analysis of minor amputations performed in patients with PVD or diabetes and the global systematic review estimated 5-year mortality rate In the range of 29-69% (Thorud et al., 2016). Despite minor amputation being viewed as a preventative procedure, mortality was still high and as such, should be viewed as a significant event in a person's disease course.

The main dependant variable of interest within the study was the effect of diabetes status on mortality risk over time. The effect of diabetes on amputation risk was found to be time dependant. This is in keeping with other studies in the literature with diabetes showing a similar (Aulivola et al., 2004; Mayfield et al., 2001; Subramaniam et al., 2005) or reduced risk (Icks et al., 2011; Pohjolainen & Alaranta, 1998) of mortality in the short-term but an increased risk of mortality in the long-term. Although the literature is not consistent and some studies report no increased risk of mortality associated with diabetes in any time period (Thorud et al., 2016). This could be due to differences in the methods used but it could reflect differences in population structure or even clinical practice and requires further exploration. The association between diabetes and mortality following major amputation was only significant for BKA. There is suggestion from the analysis that this is due to the frailty of the population in which AKA is performed in. There are few studies and no population-based studies that have explored the effect of diabetes on mortality following major amputation stratified by level to compare to. These findings reflect that these procedures occur in the most unwell in both populations, mitigating the effect of diabetes.

8.7 Clinical significance

The prevalence of diabetes is set to increase within Wales and the rest of the world due to an ageing population and the rising prevalence of obesity. Within Wales the risk factors for and

the prevalence of diabetes is the highest in the UK. The cost of diabetes and in particular diabetic foot disease on the NHS in Wales is already considerable. If the incidence of foot disease doesn't decrease the economic and social cost will be untenable. This is especially true when large volumes of the amputations are preventable. It is important to understand the current disease burden to assess the effects off future change and where interventions are required most urgently. This is the first study to quantify amputation rates for the whole of Wales and by region for both the population with and without diabetes. There was variance in amputation rates between health boards and variance from gold standards of care for diabetic foot disease. By highlighting variance in care this provides the grounds for interventions to improve patient care.

8.8 Future work

The RCA, secondary care, and SAIL data, identified that that a large number of patients undergoing amputation had a history of PVD. This was associated with a greater risk of mortality in the last analysis. In both populations with and without diabetes less that 35% of patients had undergone revascularisation procedures despite this being the only risk factor independently associated with a reduced risk of mortality following major amputation. Within the health board and population analysis it was identified that a smaller proportion of patients with diabetes underwent vascular procedures despite having a greater prevalence of PVD. NICE guidance (NICE, 2018) recommends attempting limb salvage procedures prior to amputation for PVD therefore the number of procedures performed within the data seems low. With limb salvage procedures the only modifiable risk factor within the mortality analysis to infer a survival benefit, this could be an area for further research within this population along with other aspects of preoperative and preventative care. It would be important to understand the prevalence of vascular procedures performed in Wales, if this was in keeping with guidelines and if this varied with diabetes status, deprivation, and location. This study only explored the survival benefit of revascularisation in those undergoing amputation which is not the whole picture. Revascularisation procedures are associated with their own mortality and exploring the variance between these groups in the population with diabetes would help gain a better insight into this complex issue.

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Appendix I - Ethical approvals

(i) Approval Chapter 3

Trauma & Orthopaedic Department
Morriston Hospital
Swansea
SA6 6NL

Our Ref: CT/5.8.21

Contact: Nicola Marsh (Secretary)
Direct Line: [redacted]
Fax:
Email: [redacted]

Jennifer Hayes
Clinical Fellow

To Whom it may concern,

RE: Investigation of diabetic foot ulceration and the cause analysis performed and evaluation of the service

I write in support of Jennifer Hayes and her thesis

At the beginning of the project we wrote to the ethics committee regarding the project and whether any ethics approval would be required or whether this was purely service evaluation

The outcome from the team was that this was a service evaluation and no formal ethics approval was required.

Unfortunately despite searching, I am unable to find the original letter but vouch professionally that this was the in place prior to the work going ahead

If you have any further questions then please do not hesitate to contact me

Your sincerely,

Dictated not signed

Miss Claire Topliss, MB BS FRCS FRCS (Tr&Orth) MD
Consultant Orthopaedic Surgeon

(ii) Approval Chapter 4

Jeffrey Stephens (Swansea Bay UHB - Diabetes)

From:	Penny Beresford (BSC - LREC)
Sent:	31 December 2015 11:57
To:	Claire Topliss (ABM ULHB - Orthopaedics)
Cc:	Jennifer Hayes (ABM - General surgery); Jeffrey Stephens (ABM ULHB - Diabetes); Rosalyn Thomas (ABM ULHB - Podiatry)
Subject:	Patient Journey into Secondary Care - Diabetic Feet at Risk

Dear Dr Topliss, thank you for your letter seeking advice regarding the above which has been considered by our Vice Chair. Based on the information provided, we are of the opinion that this is an evaluation of clinical practice designed to improve the delivery of service by that particular team of health professionals, and is not considered to be research. If this interpretation is correct and there are no plans to publish the data obtained from the project or to promote it as a research project in any way we would advise that this project would not require ethical review, however, should this not be the case, then the project would require ethical review in the usual way.

With best wishes for the New Year,
Kind regards,
Penny

Penny Beresford
REC Manager / Rheolwr y Gwasanaeth Moeseg

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Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

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(iii) Approval Chapter 5

Engaging with non-attenders to diabetic foot screening.

Anne-Claire Owen (ABM ULHB - Research & Development Department) <[redacted]>

Mon 20/11/2017 10:11

To: Stephens J.W. <[redacted]>

Title: Engaging with non-attenders to diabetic foot screening

Dear Jeff

Apologies again for the delay in the review of the above project. The project was reviewed with the Chairman of the Joint Study Review Committee (JSRC) and I can confirm that we consider this project to be a 'non-research' on the basis that the aim is to find out what has made people in this sample not take up foot care and that the additional activities participants will be asked to undertake are not intrusive. In publishing your results please confirm that the project was considered to be 'non-research' not requiring a R&D application.

I note that you have the support of the appropriate Health Board Clinical Directors.

Good luck with the project.

Best wishes
Anne-Claire

Anne-Claire Owen
Assistant Manager | Research & Development | ABMU Health Board
Rheolwr Cynorthwyol | Ymchwil a Datblygu | Bwrdd Iechyd PABM

Abertawe Bro Morgannwg University Health Board / Bwrdd Iechyd Prifysgol Abertawe Bro Morgannwg
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☏ [redacted] | 🖷 [redacted] ✉ [redacted]

We constantly strive to improve our services and value your feedback. We'd really like to hear from you and

Service evaluation/Quality Improvement project in Diabetes Care.

Amendment to Summary proposal – Engaging with non-attenders to diabetic foot screening.

Dr Jenny Hayes, Prof Jeffrey Stephens, Diabetes Centre, Morriston Hospital.

(In collaboration with Clydach Health Practice, ABMU Health Board)

As outlined in the previous proposal submitted to the JRCF we are interested in evaluating and understanding the current diabetic clinical foot care service within the health board. It has been a challenge to correspond with patients who have chosen not to attend clinics and foot care. With an aim to establish tools to identify patients with diabetes at risk of foot disease and tailor our service to high-risk individuals. As part of this we aimed to address non attendance, an issue highlighted in a root cause analysis of our service. Although we made provision for the difficult nature of contacting these patients, this has proved more difficult than anticipated. The work is clinical service delivery.

With the rate of amputation in the health board the highest in Wales, we feel it is important to continue to review our current service. Therefore we would like to explore patients views on education in our current clinical service. NICE and Diabetes UK both highlight foot care education as an integral role in management of diabetic foot disease. Although guidance on diabetic foot care is an expectation every time a patient engages with the diabetic service, this has never been explored within the health board.

We aim to approach patients during a four-month period from the Secondary Care diabetes service or from a local Primary Care Practice (Clydach). Patients will be approached during their regular diabetic review in primary or secondary care whilst waiting for clinical review. Their general views and knowledge on diabetic foot care will be explored by open questions. We will then explore patients perceptions of the current service and patients expectations and ideas on what the service should provide. Patient based focus groups and diabetes education-based groups are routine within our service delivery model.

This may then lead to empirical interventions based on patients perceived needs and establish the suitability and feasibility of this type of risk reduction approach for patients with diabetic foot disease.

We believe this is service delivery based work as per the previous proposal.

RE: Query For JSRC review.

Anne-Claire Owen (ABM ULHB - Research & Development Department) <[redacted]

Tue 19/06/2018 10:13

To: Stephens J.W. <[redacted]

Dear both

Thank you for submitting the amendment for the project **Engaging with non-attenders to diabetic foot screening,** which has been reviewed within the Department and the JSRC Chairman. I am pleased to confirm that we consider the project remains a 'non-research/service evaluation' project.

Best wishes
Anne-Claire

Anne-Claire Owen
Assistant Manager | Research & Development | ABMU Health Board
Rheolwr Cynorthwyol | Ymchwil a Datblygu | Bwrdd Iechyd PABM

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☏ [redacted]

From Monday 16 April 2018, the submission process for studies and amendments in Wales is changing. Read more here.

We constantly strive to improve our services and value your feedback. We'd really like to hear from you and your responses will, of course, remain confidential and you won't be identified in any results. Please click on this link to leave your feedback: www.healthandcareresearch.gov.wales/your-views/

Rydyn ni bob amser yn ymdrechu i wella ein gwasanaethau ac rydyn ni'n gwerthfawrogi'ch adborth. Fe fydden ni'n wirioneddol hoffi clywed oddi wrthych chi ac fe fydd eich ymatebion, wrth gwrs, bob amser yn gyfrinachol ac ni fyddwn ni'n eich enwi mewn unrhyw ganlyniadau. Cliciwch ar y ddolen hon i roi'ch adborth: www.ymchwiliechydagofal.llyw.cymru/your-views-cy

From: Stephens J.W. [redacted]>
Sent: 06 June 2018 08:22
To: Anne-Claire Owen (ABM ULHB - Research & Development Department) <[redacted]>; Jen Hayes [redacted]
Subject: Fw: Query For JSRC review.

Hello AC

We have prepared a slight amendment to the attached proposal which was approved by the JSRC as service delivery work.
I have attached a page of amendment. We all feel that this remains service delivery. Not sure if this needed to come back to you. I have attached the 1 page amendment. Is this ok?

BW

Jeff

Jeffrey W Stephens BSc, MB BS, PhD, FRCP, FAcadMEd, FHEA
Clinical Professor of Diabetes, School of Medicine, Swansea University
Consultant Physician, Morriston Hospital, ABMU Health Board
AMD Medical Education, ABMU Health Board

Address: Diabetes Research Group, [redacted], Swansea University, Swansea SA2 8PP, Wales, UK
Tel: [redacted]

From: Stephens J.W.
Sent: 09 October 2017 15:15
To: Anne-Claire Owen (ABM ULHB - Research & Development Department)
Subject: FW: Query For JSRC review.

Hello AC

Please find attached the proposal for review in JSRC.

You'll see from the e-mails below comments from David Price (CD Medicine) and Richard Tristham (CD for Primary Care) in support of the service-nature of this work. I also have an e-mail from Steve Bain and can forward if need be,

I have managed to make a pdf from their e-mails confirming the service nature/quality improvement nature of the work (and is attached).

BW

Jeff

Jeffrey W Stephens BSc, MB BS, PhD, FRCP, FAcadMEd
Clinical Professor of Diabetes, School of Medicine, Swansea University
Consultant Physician, Morriston Hospital, ABMU Health Board
AMD Medical Education, ABMU Health Board

Address: Diabetes Research Group, [redacted], Swansea University, Swansea SA2 8PP, Wales, UK
Tel: [redacted]

From: David Price (ABM ULHB - Medicine) [redacted]]
Sent: Monday, October 09, 2017 1:57 PM
To: Stephens J.W.; Bain S.C.; Richard Tristham (Clydach - Clydach Health Centre)
Subject: RE: Query

Jeff

I support this as service delivery

David

From: Stephens J.W. [redacted]
Sent: 09 October 2017 09:53
To: David Price (ABM ULHB - Medicine); Bain S.C.; Richard Tristham (Clydach - Clydach Health Centre)
Subject: Fwd: Query

Hello all

Further to my e-mail last week, are you ok to support this as a service evaluation/quality improvement project? Would be of use in your CD roles, for me to take to the JSRC.

If so would you be able to send me a 'new' e-mail Supporting this? I can then submit to the JSRC for approval. Apologies, but I'm trying to nail this today.

BW

Jeff

Sent from my iPhone

Begin forwarded message:

> **From:** Jennifer Hayes [redacted]>
> **Date:** 9 October 2017 at 09:36:30 BST
> **To:** Stephens J.W. [redacted]
> **Subject: Re: Query**
>
> Hi Prof Stephens,

Please find attached the summary proposal for the JSRC. Let me know if I need to add more.

BW
Jenny

On 6 October 2017 at 12:24, Stephens J.W. <[redacted]> wrote:
No worries..

I'll then 'tweak' and send to AC..

Have a nice weekend.

BW

Sent from my iPhone

On 6 Oct 2017, at 12:22, Jennifer Hayes [redacted]> wrote:

> Hi Prof Stephens.
>
> Yeah no problem. Is it ok if I get it to your for Monday?
>
> Thanks,
> Jenny
>
> Sent from Mail for Windows 10
>
> ---
>
> **From:** Stephens J.W.
> **Sent:** 06 October 2017 12:04
> **To:** Jen Hayes
> **Subject:** Fwd: Query
>
> Hi Jen
>
> FYI.
>
> Would you mind draft? We could submit from me??
>
> Jeff
>
> Sent from my iPhone
>
> Begin forwarded message:
>
> > **From:** "Anne-Claire Owen (ABM ULHB - Research & Development Department)" <[redacted]>
> > **Date:** 6 October 2017 at 11:58:55 BST

To: 'Stephens J.W.' [redacted]>
Subject: RE: Query

Hi Jeff

Yes, a 1-2 page summary would be great. These are being reviewed at the JSRC Sub Committee now - next meeting is 18 October, if you could get the information to me by next Wednesday 11 October I'll ensure its included for review.

Let me know if there's anything else – POW today but back in ILS2 on Monday.

BW
AC

From: Stephens J.W. [redacted]
Sent: 05 October 2017 11:41
To: Anne-Claire Owen (ABM ULHB - Research & Development Department) <[redacted]
Subject: Query

Hi AC

We have a project which Steve and I think is Service Delivery. What do the JSRC need to approve? Is it a page summary?

BW

Jeff

Cymraeg;-
Mae'r neges hon yn gyfrinachol. Os nad chi yw'r derbynnydd y bwriedid y neges ar ei gyfer, rhowch wybod i'r anfodydd yn ddioed. Dylid ystyried unrhywd ddatganiadau neu sylwadau a wneir uchod yn rhai personol, ac nid o angenrhiad yn rhai o eiddo Bwrdd Iechyd Prifysgol Abertawe Bro Morgannwg, nac unrhyw ran gyfansoddol ohomi na chorff cysylltiedig. Cofiwch fod yn ymwybodol ei bod yn bosibl y bydd disgwyl i Fwrdd Iechyd Prifysgol Abertawe Bro Morgannwg roi cyhoeddusrwydd i gynnwys unrhyw e-bost neu ohebiaeth a dderbynnir, yn unol ag amodau'r Ddeddf Rhyddid Gwybodaeth 2000. I gael rhagor o wybodaeth am Rhyddid Gwybodaeth, cofiwch gyfeirio at wefan Bwrdd Iechyd Prifysgol Abertawe Bro Morgannwg yn

(iiii) Approval Chapter 6&7

Professor Jeffrey Stephens

Swansea University Medical School

Singleton Park

Swansea

SA2 8PP

Dear Jeffrey,

Re: Prevention of major amputations secondary to diabetic foot disease

Your proposal to use the SAIL databank has been assessed by the SAIL Collaboration Review System (CRS). The CRS consists of the SAIL Management Team and the Information Governance Review Panel (IGRP). The membership of the IGRP is comprised of senior representatives from:

- British Medical Association (BMA)
- National Research Ethics Service (NRES)
- Public Health Wales
- NHS Wales Informatics Service (NWIS)
- Abertawe Bro Morgannwg University Health Board (ABMU)
- Consumer Panel for Data Linkage Research

After careful consideration the proposal has been given **approval** to commence with analysis.

The project has been given a SAIL project number of **0716.** Please quote this number in all correspondence regarding this project.

Creation of project specific data view

Work will now commence on the creation of the project specific data view. The lead analyst contact for this will be Caroline Brooks and they will be in contact with you to confirm your data specification.

SAIL DATABANK

Data Science Building

Medical School

Swansea University

Singleton Park

Swansea

SA2 8PP

User access

Once the project specific data view has been created you will be allocated a SAIL Gateway user account if you require direct access to the data. Please contact [redacted] for details of how to apply for an account.

Publication statement

Appendix II - Chapter 3 documents

(i) GP and patient letters

Letter 1: GP Letter request for RCA - deceased patients

Dear Doctor

Serious Adverse Event Review:

Name Details etc

Deceased

I write on behalf of the multidisciplinary foot service in Morriston Hospital and would like to ask for your help in providing information on the above patient.

The above patient underwent a major lower limb amputation in 2015 and as a group we are investigating the events leading up to the amputation. This project is in response to the fact that in ABMU HB we have the highest amputation rates (per population) in Wales, despite not having the highest rates of diabetes prevalence. Work in multiple centres across the UK has shown that it is possible to reduce major amputation rates by up to 80%. We are aware that the patient journey to such an event is often long and complex and that we are likely to identify a number of system areas in which improvement can be made, your help in identifying areas for improvement would be invaluable.

As part of the patient's team we would value review of their primary care journey so that we can make a comprehensive evaluation. This is not aiming to be a 'witch hunt' but a review for patient benefits in the future. In identifying system problems we hope to invest and improve these areas. I have enclosed an information sheet which is amended from that available at Diabetes UK. It has been used in similar assessments across the UK.

As the patient is now deceased, we have not included a patient consent.

We thank you in anticipation for your co-operation in this project and look forward to informing you of the results after completion of the review.

With thanks

Alastair Roeves (Medical Director Primary Care, ABMU HB)

Claire Topliss (Consultant Orthopaedic Surgeon)

Colin Ferguson (Consultant Vascular Surgeon) on behalf of the Vascular Team

David Price (Consultant Diabetologist) on behalf of the Diabetes Team

Letter 2: GP Letter request for RCA

Dear Doctor

Serious Adverse Event Review:

Name Details etc

I write on behalf of the multidisciplinary foot service in Morriston Hospital and would like to ask for your help in providing information on the above patient.

Your patient underwent a major lower limb amputation in 2015 and as a group we are investigating the events leading up to the amputation. This project is in response to the fact that in ABMU HB we have the highest amputation rates (per population) in Wales, despite not having the highest rates of diabetes prevalence. Work in multiple centres across the UK has shown that it is possible to reduce major amputation rates by up to 80%. We are aware that the patient journey to such an event is often long and complex and that we are likely to identify a number of system areas in which improvement can be made, your help in identifying areas for improvement would be invaluable.

As part of the patient's team we would value review of their primary care journey so that we can make a comprehensive evaluation. This is not aiming to be a 'witch hunt' but a review for patient benefits in the future. In identifying system problems we hope to invest and improve these areas. I have enclosed an information sheet which is amended from that available at Diabetes UK.

Attached is a copy of the patient consent to facilitate review of their records.

We thank you in anticipation for your co-operation in this project and hope to inform you of the results after completion of the review.

With thanks

Alastair Roeves (Medical Director Primary Care, ABMU HB)

Claire Topliss (Consultant Orthopaedic Surgeon)

Colin Ferguson (Consultant Vascular Surgeon) on behalf of the Vascular Team

David Price (Consultant Diabetologist) on behalf of the Diabetes Team

Letter 3: Patient letter for consent

Dear

Service Review into Major Amputation – Morriston Hospital, ABMU HB

Following your amputation in 2015, a group of clinical staff would like to review your case to review your treatment. This would enable us to look at ways in which we can improve the process for patients in the future.

We would like to ask for your help in this process:

- First of all we would like to register your agreement for us to perform the review and would be grateful if you could sign the attached form and send it back in the enclosed stamped addressed envelope. This form will allow us to look at your hospital and general practice records to get a full picture of your journey.
- Secondly we would be grateful if you could give us comments on your pathway to help us identify areas where we could make improvements.

We look forward to hearing from you in the near future

Many thanks

Claire Topliss (Consultant in Trauma and Orthopaedics)

Colin Ferguson (Consultant Vascular Surgeon) on behalf of the Vascular Team

David Price (Consultant Diabetologist) on behalf of the Diabetes Team

Letter 4: Patient consent form

Amputation Review Consent Form

I _____ (patient name) _____(Date of Birth) agree that the clinical team in Morriston Hospital can review my hospital records to review my treatment/management and identify service improvements for future patients.	
Signed:	Date:
I agree that the team can contact my General Practitioner (GP) for information from my practice notes which will also help in this process.	
Signed:	Date:
I do not consent to the clinical team contacting my GP for information.	
Signed:	Date:
Additional Comments:	

(ii) Data entry form

Amp RCA: Summary	
RCA No:	**NHS No:**
GP Practice:	
Date/time/location of the major amputation	
Date patient admitted to MH	
Amputation type	
Primary Diagnosis (PVD/ Osteomyelitis/Sepsis)	
Name of person completing the chronology	
Additional Comments:	

Summarise with Possible Causal Factors	
Patient	
Staff	
Task	
Communication	
Equipment	
Work Conditions	
Organisation	
Education & Training	
Team	

Amp RCA: Front Sheet & Check List

NHS No			
RCA No			
Consent for GP Record Access	Yes	No	Presumed
GP Pathway	Accessed	Not Available	Signed
Community Pathway	Accessed	Not Available	Signed
Podiatry Access	Accessed	Not Available	Signed
Hospital Notes	Accessed	Not Available	Signed
Pathology Records Biochem Micro	Accessed	Not Available	Signed
Radiology	Accessed	Not Available	Signed
Put on Electronic Record	Date:		Signed
Label Sheet Attached	Yes	No	Signed

Amp RCA: Chronology Template				
RCA No:		**NHS No:**		
Event Date & Time	**What actually happened**	**Missing info / gaps**	**Good practice identified**	**Problems identified**

Amp RCA: Podiatry Data Collection		
RCA No:	**NHS No:**	
Are communications from community podiatry and secondary care for diabetic foot patients adequate i.e. detailed care plan, identification or risk?	Yes	No
What was the referral to treatment times within podiatry - 24 to 48 hours for a wound or longer?	Yes	No
In this specific case: what was the foot risk score at the last routine foot check prior to this episode?	Yes	No
Was preventative nail cutting and debridement of callus for those with diabetic risk provided before the ulceration occurred? Were risk factors assessed, documented and acted on when they were identified?	Yes	No
Was individual known to podiatry prior to this episode? If so, were they under regular podiatry review?	Yes	No
When this individual first presented with a foot wound how long until presentation to foot team?	Yes	No
On classification of an increased risk foot, did referral occur?	Yes	No
Did the patient get referred quickly when they were determined to be at risk of diabetic foot ulceration?	Yes	No
When a patient presents with corns/ callus, was appropriate treatment offered and was the advice/care appropriate in terms of frequency?	Yes	No
Were prevention strategies employed to prevent ulceration?	Yes	No
Was there the provision of insole/ orthotic provision and return times?	Yes	No
Was vascular /neurological status checked? Was the patient educated about risk factors such as smoking etc?	Yes	No
Did the patient receive education on risk of developing foot ulcers?	Yes	No
Had podiatry undertaken vascular assessments and neurological assessments according to NICE guidance?	Yes	No

Was the patient seen with a frequency appropriate to need?	Yes	No
Had the patient been offered diabetic foot education or advice?	Yes	No
Were signs of deteriorating foot ulcers recognised and onward referrals made promptly?	Yes	No

Chronology of Podiatry Events

Event Date & time	What actually happened	Missing information/gaps	Good practice identified	Problems identified

Additional Comments	

Amputation RCA: Primary Care Data Collection				
RCA No:			**NHS No:**	
Arterial Disease		Yes	No	FH
Neuropathic Disease		Yes	No	Unknown
BP controlled	Yes	No	When	Meds
Cholesterol controlled	Yes	No	When	Meds
Smoker	Yes	No	Ex / When	Attempts at cessation?
BMI	Number	Acceptable	Overweight	Obese
Any weight interventions	Yes	No	What	
Diabetes	Type 1	Type 2	Diagnosis Date	
Sugars controlled	Yes	No	Last HbA1c?	
Date of last annual review?				
Annual Foot checks done?		Yes	No	Last visit?

Foot Risk stratification	Yes		No	
	Active	High	Moderate	Low
Appropriate intervals for foot check? Ref – Putting Feet First	Yes	No		
Any abnormality noted	Yes	No	What?	
Appropriate Referral?	Yes	No	Why not?	
Where referred?	Speciality:		Any Delay?	

Interventions:

Date	Intervention	Response

How was patient compliance with treatments/interventions?			
Previous ulceration?	Yes	No	Outcome
Previous minor amputation	Yes	No	Comment:
Additional Comments:			

System Factors:		Comments:
Is there a standard operating procedure for diabetic foot examination at annual diabetic review?	Yes	
	No	
Are all members of staff undertaking the diabetes annual foot check trained to examine and record risk status	Yes	
	No	
Is each patient advised about foot care at each annual review	Yes	
	No	
Does the practice have written foot care information for patients at diabetic annual review?	Yes	
	No	
Is every patient at high risk of diabetic foot ulceration referred to community podiatry for regular review?	Yes	
	No	
Is the practice conversant with pathways for referral of high risk and ulcer patients to podiatry and secondary care?	Yes	
	No	
Are communications from community podiatry and secondary care for diabetic foot patients adequate?	Yes	
	No	

Amp RCA: Secondary Care Data Collection					
RCA No:			**NHS No:**		
PostCode		HD	ABMU	Other	
GP Practice					
Gender		Male		Female	
Residential Status		Own home	Residential home	Nursing home	Other
Marital status		Married/Partner		Single	
Social Support		Lives alone	Active Carer	Support available	
Admission Date					
Admission from?		Usual residence		Other Hospital	
Date of decision to transfer					
Date of transfer					
Admission Route		GP	ED	Podiatry	Other
Admission Ward					
Admission Consultant					
Admission Speciality		Vasc	Ortho	Diabet	Gen Med
Any Ward/Speciality changes?		Yes	No	What?	

Admission HbA1c				
Admission Bloods	Urea	Creat/eGFR	CRP	WCC
Major Amputation Date				
Grade of Surgeon	Consultant	SpR	Other:	
Side	Left	Right		
Amputation Level	BKA	Thru Knee	AKA	
Date of Initial Foot problem				
Site of Main Ulcer	Digit	Forefoot	Midfoot	Heel
Position of Ulcer	Plantar	Dorsal	Med/Lat	
SINBAD score when first seen			Not Done	
Waterlow Score on admission				
Any other pressure areas	Yes	No	What?	
Any offloading in place	Yes	No	What?	
Appropriate Footwear on admission	Yes	No	Comment	
Dialysis	Yes	No	How long?	
Neuropathy	Yes	No	Not known	
Charcot	Yes	No	Not known	

Medical co morbidities?			
Recent Acute Illness?	Yes	No	What?
Cancer history?	Yes	No	What?
Any Cognitive Dysfunction?	Yes	No	What?
Does Patient have mental capacity?	Yes	No	Comment
Any mobility issues?	Yes	No	What?
Seen by Diabetic Foot Care Service within 6 months of amputation	Yes When	No	Not known
Foot assessment within 24 hours of admission	Yes	No	
Foot pulses examined within 24 hours of admission	Yes	No	Not known
Was there at least one palpable pulse in the affected limb	Yes	No	Not known
ABPI / TBPI done?	Yes Ankle Toe	No	R L
Seen by DSN/Diabetologist	Yes Date	No	Not known
Regular DSN/Diabetology review?	Yes	No	Dates:
Xray performed within 24 hours of admission	Yes	No	Why not?

Antibiotics prescribed as per protocol/based on cultures/on Micro advice	Yes	No	Not known
Response to Antibiotic treatment			
Appropriate Senior Review	Yes	No	Reason?
Orthopaedic Review required	Yes	No	Comment
Date of Ortho referral?			
Date of Ortho review?			
MRI foot requested	Yes	No	Date:
MRI foot performed – Date			
Date referred to vascular			
Date of first vascular review			
Date of vascular imaging			
Date of vascular MDT			
Any revascularisation in episode	Yes	No	Not known
Date of revascularisation			
Type of revascularisation	Angioplasty	Open	

Missed chance of revascularisation		Yes	No	Comment
Patient seen by member of the MDFS within 24 hours		Yes	No	Vascular Gen Ortho Foot & Ankle Podiatry Diabetologist
Any delay in review		Yes	No	Who?
Date of first MDFS review				
1st Debridement	Date	What	Service	Grade
2nd debridement	Date	What	Service	Grade
3rd debridement	Date	What	Service	Grade
4th debridement	Date	What	Service	Grade
5th debridement	Date	What	Service	Grade
What could have been done differently?				
Did patient contribute to poor compliance?				
Any areas where the foot care pathway/other recommendations not followed				

Death in hospital?	Yes	Date of Death	
Discharged alive	Yes	Date of Discharge	
Could the amputation have been prevented	Yes	No	Possible
If yes, how?			
If no, what were the causes of the amputation			
Additional comments			

(iii) NPSA Contributory Factors Classification Framework - NPSA (Producer). (2009). Contributory Factors Classification Framework. accessed 01/09/2017

NHS
National Patient Safety Agency

Root Cause Analysis Investigation tools

Contributory Factors Classification Framework

Patient Factors	Components
Clinical condition	❑ Pre-existing co-morbidity ❑ Complexity of condition ❑ Seriousness of condition ❑ Limited options available to treat condition ❑ Disability
Physical Factors	❑ Poor general physical state ❑ Malnourished ❑ Dehydrated ❑ Age related issues ❑ Obese ❑ Poor sleep pattern
Social Factors	❑ Cultural / religious beliefs ❑ Language ❑ Lifestyle (smoking/ drinking/ drugs/diet) ❑ Sub-standard living accommodation (e.g. dilapidated) ❑ Life events ❑ Lack of support networks / (social protective factors -Mental Health Services) ❑ Engaging in high risk activity
Mental/ Psychological Factors	❑ Motivation issue ❑ Stress / Trauma ❑ Existing mental health disorder ❑ Lack of intent (Mental Health Services) ❑ Lack of mental capacity ❑ Learning Disability
Interpersonal relationships	❑ Staff to patient and patient to staff ❑ Patient engagement with services ❑ Staff to family and family to staff ❑ Patient to patient ❑ Family to patient or patient to family ❑ Family to family (Siblings, parents, children)

Staff Factors	Components
Physical issues	❑ Poor general health (e.g. nutrition, hydration, diet, exercise, fitness) ❑ Disability (e.g. eyesight problems, dyslexia) ❑ Fatigue ❑ Infected Healthcare worker
Psychological Issues	❑ Stress (e.g. distraction / preoccupation) ❑ Specific mental illness (e.g. depression) ❑ Mental impairment (e.g. illness, drugs, alcohol, pain) ❑ Lack of motivation (e.g. boredom, complacency, low job satisfaction)
Social Domestic	❑ Domestic problems (e.g. family related issues) ❑ Lifestyle problems (e.g. financial/housing issues) ❑ Cultural beliefs ❑ Language
Personality Issues	❑ Low self confidence / over confidence (e.g. Gregarious, reclusive, interactive) ❑ Risk averse / risk taker ❑ Bogus Healthcare worker
Cognitive factors	❑ Preoccupation / narrowed focus (Situational awareness problems) ❑ Perception/viewpoint affected by info. or mindset (Expectation/Confirmation bias) ❑ Inadequate decision/action caused by Group influence ❑ Distraction / Attention deficit ❑ Overload ❑ Boredom

Task Factors	Components
Guidelines, Policies and Procedures	❑ Not up-to-date ❑ Unavailable at appropriate location (e.g. Lost/missing/non-existent/not accessible when needed) ❑ Unclear/not useable (Ambiguous; complex; irrelevant, incorrect) ❑ Not adhered to / not followed ❑ Not monitored / reviewed ❑ Inappropriately targeted/focused (i.e. not aimed at right audience) ❑ Inadequate task disaster plans and drills
Decision making aids	❑ Aids not available (e.g. CTG machine; checklist; risk assessment tool; fax machine to enable remote assessment of results) ❑ Aids not working (e.g. CTG machine, risk assessment tool, fax machine) ❑ Difficulties in accessing senior / specialist advice ❑ Lack of easy access to technical information, flow charts and diagrams ❑ Lack of prioritisation of guidelines ❑ Incomplete information (test results, patient history)
Procedural or Task Design	❑ Poorly designed (i.e. Too complex; too much info.; difficult to conceive or remember) ❑ Guidelines do not enable one to carry out the task in a timely manner ❑ Too many tasks to perform at the same time ❑ Contradicting tasks ❑ Staff do not agree with the 'task/procedure design' ❑ Stages of the task not designed so that each step can realistically be carried out ❑ Lack of direct or understandable feedback from the task ❑ Misrepresentation of information ❑ Inappropriate transfer of processes from other situations ❑ Inadequate Audit, Quality control, Quality Assurance built into the task design ❑ Insufficient opportunity to influence task/outcome where necessary ❑ Appropriate automation not available

Communication	Components
Verbal communication	❑ Inappropriate tone of voice and style of delivery for situation ❑ Ambiguous verbal commands / directions ❑ Incorrect use of language ❑ Made to inappropriate person(s) ❑ Incorrect communication channels used
Written communication	❑ Inadequate patient identification ❑ Records difficult to read ❑ All relevant records not stored together and accessible when required ❑ Records incomplete or not contemporaneous (e.g. unavailability of patient management plans, patient risk assessments, etc) ❑ Written information not circulated to all team members ❑ Communication not received ❑ Communications directed to the wrong people ❑ Lack of information to patients ❑ Lack of effective communication to staff of risks (Alerts systems etc)
Non verbal communication	❑ Body Language issues (closed, open, body movement, gestures, facial expression)
Communication Management	❑ Communication strategy and policy not defined / documented ❑ Ineffective involvement of patient/carer in treatment and decisions ❑ Lack of effective communication to patients/relatives/carers of risks ❑ Lack of effective communication to patients about incidents (being open) ❑ Information from patient/carer disregarded ❑ Ineffective communication flow to staff up, down and across ❑ Ineffective interface for communicating with other agencies (partnership working) ❑ Lack of measures for monitoring communication

Equipment	Components
Displays	❑ Incorrect information / feedback available ❑ Inconsistent or unclear information ❑ Illegible information ❑ Interference/unclear equipment display
Integrity	❑ Poor working order ❑ Inappropriate size ❑ Unreliable ❑ Ineffective safety features / not designed to fail safe ❑ Poor maintenance programme ❑ Failure of general services (power supply, water, piped gases etc)
Positioning	❑ Correct equipment not available ❑ Insufficient equipment / emergency backup equipment ❑ Incorrectly placed for use ❑ Incorrectly stored
Usability	❑ Unclear controls ❑ Not intuitive in design ❑ Confusing use of colour or symbols ❑ Lack of or poor quality user manual ❑ Not designed to make detection of problems obvious ❑ Use of items which have similar names or packaging ❑ Problems of compatibility

Work Environment	Components
Administrative factors	❑ Unreliable or ineffective general administrative systems (Please specify e.g.: Bookings, Patient identification, ordering, requests, referrals, appointments) ❑ Unreliable or ineffective admin infrastructure (e.g. Phones, bleep systems etc) ❑ Unreliable or ineffective administrative support
Design of physical environment	❑ Poor or inappropriate office design (computer chairs, height of tables, anti-glare screens, security screens, panic buttons, placing of filing cabinets, storage facilities, etc.) ❑ Poor or inappropriate area design (length, shape, visibility, provision of space) ❑ Inadequate security provision ❑ Lack of secure outside space ❑ Inadequate lines of sight ❑ Inadequate/inappropriate use of colour contrast/patterns (walls/doors/flooring etc)
Environment	❑ Facility not available (failure or lack of capacity) ❑ Fixture or fitting not available (failure or lack of capacity) ❑ Single sex accommodation limitation/breach ❑ Ligature/anchor points ❑ Housekeeping issues – lack of cleanliness ❑ Temperature too high/low ❑ Lighting too dim or bright, or lack of ❑ Noise levels too high or low ❑ Distractions
Staffing	❑ Inappropriate skill mix (e.g. Lack of senior staff; Trained staff; Approp. trained staff) ❑ Low staff to patient ratio ❑ No / inaccurate workload / dependency assessment ❑ Use of temporary staff ❑ High staff turnover
Work load and hours of work	❑ Shift related fatigue ❑ Excessive working hours ❑ Lack of breaks during work hours ❑ Excessive of extraneous tasks ❑ Lack of social relaxation, rest and recuperation
Time	❑ Delays caused by system failure or design ❑ Time pressure

Organisational	Components
Organisational structure	❑ Hierarchical structure/Governance structure not conducive to discussion, problem sharing, etc. ❑ Tight boundaries for accountability and responsibility ❑ Professional isolation ❑ Clinical versus the managerial model ❑ Inadequate maintenance ❑ Lack of robust Service level agreements/contractual arrangements ❑ Inadequate safety terms and conditions of contracts
Priorities	❑ Not safety driven ❑ External assessment driven e.g. Annual Health checks ❑ Financial balance focused
Externally imported risks	❑ Unexpected adverse impact of national policy/guidance (from Department of Health / Health authorities /Professional colleges) ❑ Locum / Agency policy and usage ❑ Contractors related problem ❑ Equipment loan related problem ❑ Lack of service provision ❑ Bed Occupancy levels (Unplanned bed opening/closures) ❑ PFI related problems (Private Finance Initiative)
Safety culture	❑ Inappropriate safety / efficiency balance ❑ Poor rule compliance ❑ Lack of risk management plans ❑ Inadequate leadership example (e.g. visible evidence of commitment to safety) ❑ Inadequately open culture to allow appropriate communication ❑ Inadequate learning from past incidents ❑ Incentives for 'at risk'/'risk taking' behaviors ❑ Acceptance/toleration of inadequate adherence to current practice ❑ Ignorance/poor awareness of inadequate adherence to current practice ❑ Disempowerment of staff to escalate issues or take action

Education and Training	Components
Competence	❑ Lack of knowledge ❑ Lack of skills ❑ Inexperience ❑ Inappropriate experience or lack of quality experience ❑ Unfamiliar task ❑ Lack of testing and assessment
Supervision	❑ Inadequate supervision ❑ Lack of / inadequate mentorship ❑ Training results not monitored/acted upon
Availability / accessibility	❑ Training needs analysis not conducted/acted upon ❑ On the job training unavailable or inaccessible ❑ Emergency Training unavailable or inaccessible ❑ Team training unavailable or inaccessible ❑ Core skills training unavailable or inaccessible ❑ Refresher courses unavailable or inaccessible
Appropriateness	❑ Inappropriate content ❑ Inappropriate target audience ❑ Inappropriate style of delivery ❑ Time of day provided inappropriate

Team Factors		Components
Role Congruence	❑	Lack of shared understanding
	❑	Role + responsibility definitions misunderstood/not clearly defined
Leadership	❑	Ineffective leadership – clinically
	❑	Ineffective leadership – managerially
	❑	Lack of decision making
	❑	Inappropriate decision making
	❑	Untimely decision making (delayed)
	❑	Leader poorly respected
Support and cultural factors	❑	Lack of support networks for staff
	❑	Inappropriate level of assertiveness
	❑	Negative team reaction(s) to adverse events
	❑	Negative team reaction to conflict
	❑	Negative team reaction to newcomers
	❑	Routine violation of rules/regulations
	❑	Lack of team openness/communication with colleagues
	❑	Inadequate inter-professional challenge
	❑	Failure to seek support
	❑	Failure to address/manage issues of competence (whistle blowing)

Appendix III-Chapter 4 documents

(i) Baseline characteristics between attenders and non-attenders to foot screening

		Non attender		Attender		P value
		117		1907		
N (%)		301(14.9%)		1723 (85.1%)		
Underwent Amputation		16 (5.3%)		101 (5.9%)		0.81
Age (years)*		62 (51.5-72.5)		62 (52-72)		0.76
Men		185 (0.6%)		970 (0.6%)		0.11
Type 2 diabetes		270 (0.9%)		1352 (0.8%)		**0.005**
Duration of diabetes entry		959 (3060)		2747 (4734)		**0.005**
WIMD*						0.30
	1	95 (31.6%)		570 (33.1%)		
	2	67 (22.3%)		356 (20.7%)		
	3	65 (21.6%)		308 (17.9%)		
	4	29 (9.6%)		226 (13.1%)		
	5	45 (15.0%)		263 (15.3%)		
Smoking status						0.62
Never		140 (52.8%)		870 (51.0%)		
Ever		125 (47.2%)		836 (49.0%)		
Neuropathy			0		292	**0.005**
PVD			0		174	**0.005**
BMI (kg/m^2)*						**0.03**
Underweight		3 (1.1%)		6 (0.4%)		
Average		46 (17.2%)		239 (14.0%)		
Overweight		61 (22.8%)		510 (29.9%)		
Obese		157 (58.8%)		953 (55.8%)		
SBP (mmHg)[1]		139.9 ±20.5		140.6 ±19.1		0.64
DBP (mmHg)[1]		79.6 ±10.8		78.1 ±9.5		**0.05**
Creatinine (umol/L)*		83 (64.4-101.6)		82.8 (66.6-99.1)		0.82
Total Cholesterol (mmol/L)[1]		4.5 ±1.2		4.34 ±1.0		0.30
HbA1c (%)[1]		8.3 ±2.02		8.7 ±1.6		**0.01**

Data are presented as count (%) *Data are presented as median and IQR XData are presented as mean and standard deviation. T1DM: Type 1 Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus; WIMD: Welsh Index of Multiple Deprivation; PVD: Peripheral vascular disease; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HbA1c: haemoglobin A1c.

Appendix IIII-Chapter 5 documents

(i) Questionnaire

Exploring Diabetic Foot Care Education in ABMU Health Board

Lower limb amputations due to diabetes are the leading cause of amputation in the UK. It is thought that many of these amputations could be prevented with good diabetic care and control and part of this is by providing good education. Most of these amputations are preceded by diabetic foot ulcers and a big part of preventing ulcers developing is by regularly checking feet and shoes.

The health board is trying to improve the care it provides to patients with diabetes with regards to foot problems. As part of this we are keen to understand what foot care education we are providing to patients at present. To do this we would like to understand the experience of people with diabetes, the education they have received, current knowledge and practices and what improvements they would like to see across their services.

As part of this we have designed this questionnaire to help us understand our service and your views better. It consists of three parts and should take around 5-10minutes. We are looking for responses from people who have been diagnosed with diabetes.

Part 1: asks about you and your health in general.

Part 2: asks about your footcare knowledge and what you do to protect your feet.

Part 3 asks about what you would like to see from the service.

Answers we receive will help us to improve our services as well as being used for research to help us better understand knowledge and behaviours of people who have normal feet, ulcers and amputations. The answers will be used as part of a research degree and may be published but every effort will be made to anonymise answers.

You're free to answer one or all the sections. You have no obligation to complete the questionnaire and your answers and any comments made will remain confidential. This will not affect the care you receive.

If you would like to undertake on online version of the survey instead, please use the link or QR code below:

https://swanseachhs.eu.qualtrics.com/jfe/form/SV_1TvNvMpCD5Z8reR

<u>Part 1:</u> General Questions

Please could you answer the following questions by either circling the answer or filling up the blanks:

1.Age: ……

2.Gender: Male/Female/Other

3. What is the highest form of education you received? Primary school/ Secondary school/ University

4. Have you ever had any problems with your feet? Yes/No

5. If yes was the problem a: Foot Ulcer Y/N

Charcot foot Y/N

Peripheral vascular disease Y/N

Ischaemic leg Y/N

Other ……

6. Have you ever had an amputation? Yes/No

7. If yes was it an amputation of your: Toe or toes Y/N

Foot Y/N

Ankle Y/N

Below Knee Y/N

Above Knee Y/N

Hip Y/N

8.Who usually looks after your diabetes: GP/ Hospital

9. Have you received any education on how to looks after your feet? Yes/ No/ Unsure

10.If yes who from: Practice nurse

GP

Podiatrist

Diabetes specialist nurse

Diabetes Consultant or team

Other ……

11. Do you know your current foot risk Yes/No

<u>Part Two:</u> Questions on knowledge and education

We would like to know what you currently think about looking after your feet. Please circle the one answer which best reflects what you think at present. It's important to answer as honestly as possible. Thank you.

1. People with diabetes should take medication regularly because the are likely to get complications secondary to their diabetes

True False Don't know

2. People with diabetes should look after their feet because they may not feel a minor injury to their feet

True False Don't know

3. People with diabetes should look after their feet because wounds and infection may not heal quickly

True False Don't know

4. People with diabetes should look after their feet because they may get a foot ulcer

True False Don't know

5. People with diabetes should not smoke because smoking causes poor circulation affecting the feet

True False Don't know

6. How often do you think you should inspect your feet?

Daily Weekly Monthly Yearly

7. If you found redness/bleeding between your toes what is the first thing you do?

Speak to health care professional Leave it alone Apply cream

8. Even if you have never had a corn/ hard skin lesion, what would you do if you had one?

File down the skin Speak to a podiatrist Leave it alone

9. How often do you think your feet should be washed?

Every day Every three days Weekly

10. What temperature of water do you think you should wash your feet in?

Doesn't matter Hot Lukewarm

11. How often do you think you should inspect the inside of your footwear for objects or torn lining?

Daily Weekly Every time you put them on

12. The diabetes diet is:

a. The way most British people eat
b. A healthy diet for most people
c. Too high in carbohydrate for most people
d. Too high in protein for most people

13. Which of the following is highest in carbohydrate?

a. Baked chicken
c. Baked potato
b. Swiss cheese
d. Peanut butter

14. Which of the following is highest in fat?

a. Semi- skimmed milk
c. Corn
b. Orange juice
d. Honey

15. Which of the following is a "free food"?

a. Any unsweetened food
c. Any food labelled "sugar free"
b. Any food that is labelled "fat free" serving
d. Any food less than 20 calories per

16. HbA1c is a measure of your average blood glucose level for the past:

a. Day
c. 6-12 weeks
b. Week
d. 6 months

17. Which is the best method for home glucose testing?

a. Urine testing
b. Blood testing
c. Both are equally good

18. What effect does unsweetened fruit juice have on blood glucose?

a. Lowers it
b. Raises it
c. Has no effect

19. Which should NOT be used to treat a low blood glucose?

a. 3 hard sweets
c. 1 cup diet soft drink
b. ½ cup orange juice
d. 1 cup skim milk

20. For a person in good control what effect does exercise have on blood glucose?

a. Lowers it
b. Raises it
c. Has no effect

21. What effect will an infection most likely have on blood glucose?

a. Lowers it
b. Raises it
c. Has no effect

22. The best way to take care of your feet is to:

a. Look at and wash them each day
c. soak them for one hour each day
b. Massage them with alcohol each day
d. buy shoes a size larger than usual

23. Eating foods lower in fat decreases your risk for:

a. Nerve disease
c. Heart disease
b. Kidney disease
d. Eye disease

24. Numbness and tingling may be symptoms of:

a. Kidney disease
c. Eye disease
b. Nerve disease
d. Liver disease

25. Which of the following is usually NOT associated with diabetes:

a. Vision Problems
c. Nerve problems
b. Kidney Problems
d. Lung problems

We would like to know what you do to look after your feet. Please tick the category which best reflects what you actually do. It's important to answer as honestly as possible. Thank you.

1. Do you examine your feet?

More than once a day | Once a day | 2-6 times a week | Once a week or less

2. Do you check your shoes before you put them on?

Often | Sometimes | Rarely | Never

3. Do you check your shoes when you take them off?

Often | Sometimes | Rarely | Never

4. Do you wash your feet?

More than once a day | Once a day | Most days a week | A few days a week

5. Do you check your feet are dry after washing?

Often | Sometimes | Rarely | Never

6. Do you dry between your toes?

Always | Often | Sometimes | Rarely/Never

7. Do you use moisturising cream on your feet?

Daily | Once a week | About once a month | Never

8. Do you put moisturising cream between your toes?

Daily | Once a week | About once a month | Never

9. Are your toenails cut?

About once a week | About once a month | Less than once a month | Never

10. Do you wear slippers with no fastening?

Most of the time | Sometimes | Rarely | Never

11. Do you wear trainers?

Most of the time | Sometimes | Rarely | Never

12. Do you wear shoes with lace-up, Velcro or strap fastenings?

Most of the time | Sometimes | Rarely | Never

13. Do you wear pointed-toed shoes?

Most of the time | Sometimes | Rarely | Never

14. Do you wear flip-flops or mules?

Most of the time | Sometimes | Rarely | Never

15. Do you break in new shoes gradually?

Always	Most of the time	Sometimes	Rarely /Never

16. Do you wear artificial fibre (e.g. nylon) socks?

Most of the time	Sometimes	Rarely	Never

17. Do you wear shoes without socks/stockings/tights?

Never	Rarely	Sometimes	Often

18. Do you change your socks/stockings/tights?

More than once a day	Daily	4-6 times a week	Less than 4 times a

19. Do you walk around the house in bare feet?

Often	Sometimes	Rarely	Never

20. Do you walk outside in bare feet?

Often	Sometimes	Rarely	Never

21. Do you use a hot water bottle in bed?

Often	Sometimes	Rarely	Never

22. Do you put your feet near the fire?

Often	Sometimes	Rarely	Never

23. Do you put your feet on a radiator?

Often	Sometimes	Rarely	Never

24. Do you use corn remedies/corn plasters/ paints when you get a corn?

Often	Sometimes	Rarely	Never

25. Do you put a dry dressing on a blister when you get one?

Often	Sometimes	Rarely	Never

26. Do you put a dry dressing on a graze, cut or burn when you get one?

Often	Sometimes	Rarely	Never

Part 3: Your view

Please share any comments you have on the service and what you would like to see.

Is the education you receive on how to look after your feet good enough? Yes/ No

Comments:

Are there any changes you wish to see in the education we provide? Yes/ No

Comments:

What type of education would you like to see? i.e teaching sessions, online, pamphlets, text reminders……..

Any other comments or suggestions?

Comments:

Thank you greatly for completing this questionnaire.

Your thoughts and views are very important to us.

(ii) Differences in participant information between fully and partially completed Michigan questionnaire – number missing 85

Parameters	Full completed	Partially completed	diff
Age (years)	59.11 (57.3-60.9)	65.65 (62.57-68.73)	p0.001
Men	169 (55%)	45(54.9%)	p.0.978
Education level			P0.000
Primary School	8 (2.9%)	9 (12.9%)	
Secondary School	171 (61.1%)	50 (71.4%)	
Higher Education	101 (36.1%)	11 (15.7%)	
Diabetic foot disease	69 (22.6%)	33 (39.3%)	p.002
Self reported foot problem	104 (34.1%)	41 (48.8%)	p.014
Amputation	15 (4.9%)	2(2.4%)	P.318
Care provider			p.112
GP	83(26.5)	30(35.3)	
Hosp	230(73.5)	55(64.7	
Received foot care education	190 (63.1%)	53 (67.1%)	p.514
Know foot risk yes	132 (43.6%)	32 (39%)	p.461

(iiI) Differences in participant information between fully and partially completed behaviour questionnaire – number missing 26

Parameters	Full completed	Partially completed	diff
Age (years)	60.23 (58.6-61.9)	64.4 (59-69.8)	p.197
Men	199 (54.8%)	15 (57.7%)	p.776
Education level			p.185
Primary School	17(5.2%)	0(0)	
Secondary School	204(62)	17(81)	
Higher Education	108(32.8)	4(19)	
Diabetic foot disease	93(25.6%)	9(34.6%)	p.314
Self reported foot problem	132 (36.4%)	13 (50%)	p.165
Amputation	17(4.7%)	0(0%)	p.261
Care provider			p.128
GP	109 (29.3%)	4(15.4%)	
Hosp	263 (70.7%)	22(84.6%)	
Received foot care education	229(64.5%)	14(56%)	p.392
Know foot risk yes	155(43.1%)	9(36%)	p.490

Appendix V-Chapter 6&7 documents

ICD 10 codes
history of limb salvage procedures, HTN, ESRD, MI, CVA, congestive cardiac failure (CCF), PVD
(i) History of limb salvage procedures

Anatomical subgroup	OPCS-4 codes
Extra-anatomical bypass	L16
Iliac bypass	L20.6, L21.6, L50, L51, L52, L65.2
Iliac angioplasty	L54
Femoroproximal bypass	L58.1, L58.2, L58.3, L59.1, L59.2, L59.3, L60
Femorodistal bypass	L58.4, L58.5, L58.6, L58.7, L59.4, L59.5, L59.6, L59.7
Femoral angioplasty	L63.1, L63.5, L63.8, L63.9
Unspecified lower limb angioplasty	L66.2, L66.5, L66.7, L66.8, L66.9, L71.1, L71.5, L97.2

(ii) Comorbidities other than ESRD

Comorbidity	ICD-10 codes
Cerebrovascular accident	G45, G46, I60–I69
Congestive cardiac failure	I11, I13, I255, I42, I43, I50, I517
Hypertension	I10, I11, I12,I13,I15
Myocardial infarction	I21*, I22*, I23*, I252
Peripheral vascular disease	I70–I73, I770, I771, K551, K558, K559, R02, Z958, Z959

(iii) ESRD - End Stage Renal Disease Detected in Hospital Admission as per UK Biobank protocol (UK Biobank, 2017b)

Step 1:

ICD 10 and OPCS 4 codes from hospital admissions are used to create variable categories that identify participants who received any RRT (and within this category those who received a kidney transplant or peritoneal dialysis which was assumed to be for maintenance RRT), and those with indicators of CKD stage 5:

Indicator	ICD-10/OPCS-4 codes
Renal replacement therapy	E85.3, N16.5, T82.4, T86.1, Y60.2, Y61.2, Y62.2, Y84.1 , Z49.0, Z49.1 ,Z49.2, Z94.0, Z99.2, M01.2, M01.3, M01.4, M01.5, M01.8, M01.9, M08.4, M17.4, M17.8, M17.9, X40.1, X40.2, X40.3, X40.4, X40.5, X40.6, X40.7, X40.8, X40.9, X41.1,X41.2, X41.8, X41.9, X42.1, X42.8, X42.9, X43.1
Renal replacement therapy maintenance	N16.5, T86.1, Z49.2, Z94.0, M01.2, M01.3, M01.4, M01.5, M01.8, M01.9, M08.4, M17.4, M17.8, M17.9, X40.2, X40.5, X40.6, X41.1,X41.2
CKD 5 indicator	E85.3, N16.5, N18.0, N18.5, T86.1, Z94.0, L74.1, L74.2, L74.3, L74.4, L74.5, L74.6, L74.8, M01.2, M01.3, M01.4, M01.5, M01.8, M01.9, M02.3, M08.4, M17.2, M17.4, M17.8, M17.9, X40.2, X40.5, X40.6, X41.1,X41.2

Step 2: ICD 10 and OPCS 4 codes are combined to create the following Derived Phenotypic Variables (DPVs).

DPV Category	Description	Rules
DPV_COMPOSITE_ANY_RRT	Any renal replacement therapy (RRT: dialysis or transplantation), i.e. includes both acute or maintenance RRT	Any participant with RRT =1 should be considered DPV_COMPOSITE_ANY_RRT=1. For this outcome, first and any subsequent records need to be recorded with all the relevant dates.
DPV_COMPOSITE_ESRD_TX_OR_PD	CKD stage 5 treated by transplantation or peritoneal dialysis	Any participant with MAINTENANCE_RRT=1 should be considered DPV_COMPOSITE_ESRD_TX_OR_PD=1. Use the earliest date of these records as the date.
DPV_COMPOSITE_CKD5_INDICATOR	Any CKD stage 5 indicator	Any participant with CKD5_INDICATOR=1; should be considered DPV_COMPOSITE_ CKD5_INDICATOR = 1. For this outcome, first and any subsequent records need to be recorded with all the relevant dates.

Step 3: Participants without evidence of a CKD stage indicator are excluded (i.e. those with acute kidney injury are excluded).

DPV Category	Description	Rules
DPV_COMPOSITE_ESRD_ONRRT	CKD stage 5 treated with renal replacement therapy identified using CKD stage 5 indicators	A record of DPV_COMPOSITE_ANY_RRT = 1 with (a) a record in DPV_COMPOSITE_CKD5_INDICATOR = 1 before the record in DPV_COMPOSITE_ANY_RRT=1, OR (b) a record in DPV_COMPOSITE_CKD5_INDICATOR = 1 on or within 365 days of the record in DPV_COMPOSITE_ANY_RRT = 1. - Use the earliest date of a record in DPV_COMPOSITE_ANY_RRT = 1 that fulfills one of these criteria as the date.
DPV_COMPOSITE_ESRD_ONRRT_COMBINED	Combined CKD stage 5 treated with RRT	Any participant with DPV_COMPOSITE_ESRD_TX_OR_PD = 1 or DPV_COMPOSITE_ESRD_ONRRT = 1. Use the earliest date of these records as the assigned case date.

Step 4: Any participant with DPV_COMPOSITE_ESRD_ONRRT_COMBINED=1 after implementation of the above algorithm steps is deemed to be an ESRD case detected by hospital admission EHRs.

Appendix VI-Clinical outcomes

Dyddiad/Date: 26th May 2018

☎ [redacted]
☎ WHTN (…)
[redacted]

Miss C Topliss
Consultant Orthopaedic Surgeon
Morriston Hospital
Swansea
SA6 6NL

Dear Miss Topliss

Root Cause Analysis Report

On behalf of the Vascular Surgery Steering Group, we would like to convey our thanks to you and your team for the hard work and effort put into the root cause analysis and the report that we have received. This report went before this group on the 25th May and was well received and there was detailed discussions around its content.

Each of the recommendations outlined in the report have been assigned to either by the Limb at Risk Task & Finish Group or to members of each of the Health Boards to be progressed. We are currently now looking into piloting a multi-disciplinary clinic on one site as well as piloting a telemedicine service in Bronglais Hospital. Neil Miles mentioned that he is in discussion with you about a special clinic within ABMU.

Furthermore, prior to Colin's retirement he attended Hywel Dda's Quality and Safety Committee where he presented on the network, the NVR data as well as a compelling story of the findings from this report which was well received by our members.

Once again we would like to thank you for the report.

With kind regards
Yours sincerely

Mr J Teape,
Deputy Chief Executive (Hywel Dda Health Board)
Co-chair of Vascular Surgery Steering Group