ESC European Society of Cardiology

European Heart Journal Open (2022) **2**, 1–12
https://doi.org/10.1093/ehjopen/oeac066

ORIGINAL ARTICLE
Epidemiology and prevention

Identifying unmet antithrombotic therapeutic need, and implications for stroke and systemic embolism in atrial fibrillation patients: a population-scale longitudinal study

Fatemeh Torabi †, Daniel E. Harris†, Owen Bodger, Ashley Akbari, Ronan A. Lyons, Michael Gravenor‡, and Julian P. Halcox *‡

Population Data Science, Swansea University, Swansea SA2 8PP, UK

Received 8 July 2022; revised 15 September 2022

Handling Editor: Magnus Bäck

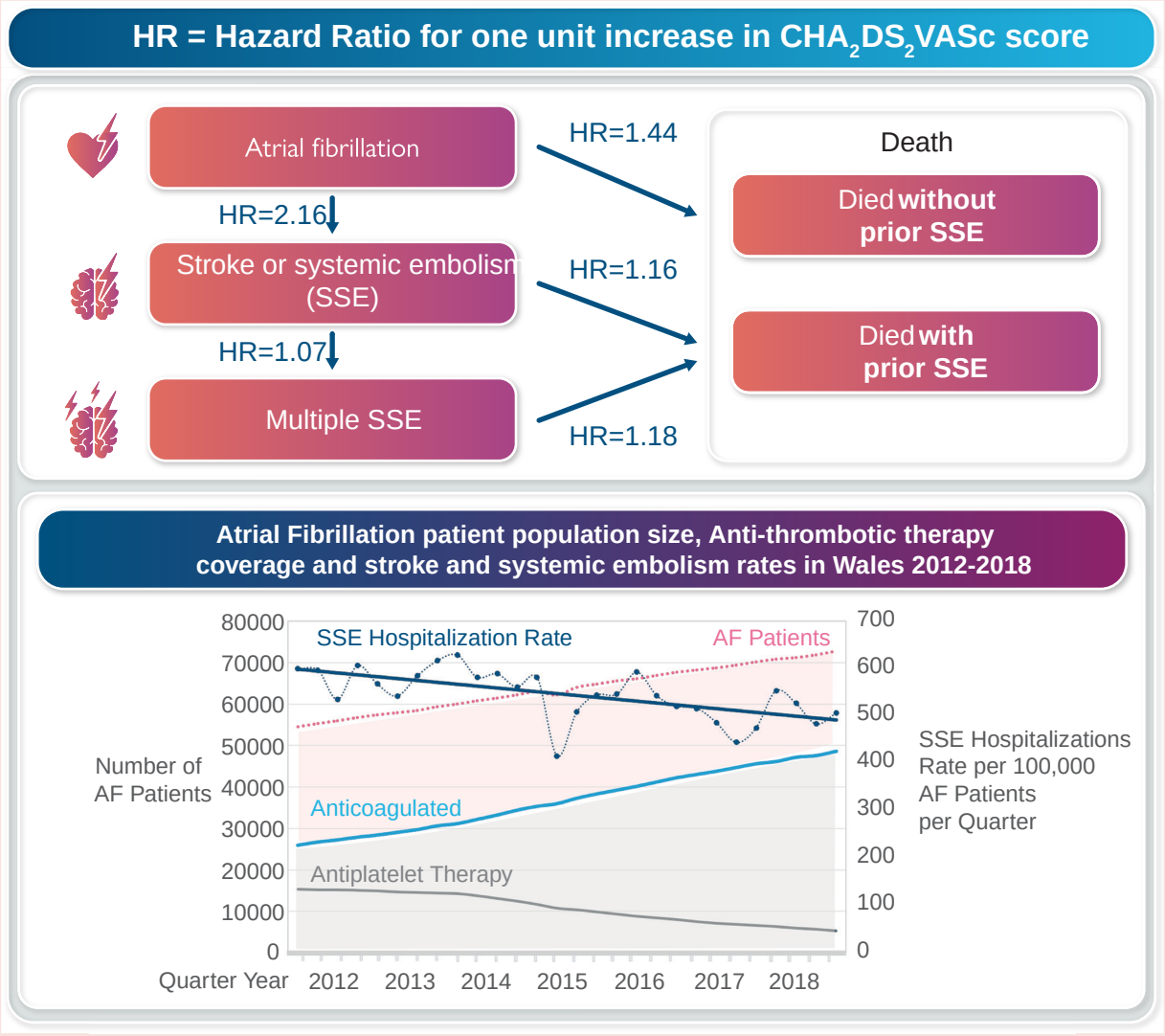
Aims Guidelines recommend anticoagulation (AC) in atrial fibrillation (AF) to reduce stroke and systemic embolism (SSE) risk; however, implementation has been slow across many populations. This study aimed to quantify the potential impact of changing prevalence of AF, associated risk, and AC prescribing on SSE hospitalizations and death.

Methods and results We evaluated temporal trends of AF, CHA_2DS_2-VASc, antithrombotic prescriptions, SSE hospitalizations, death, and their associations between 2012 and 2018 in a longitudinal cohort of AF patients in Wales UK. Multi-state Markov models were used to estimate expected SSE rates given the AC coverage, adjusting for CHA_2DS_2-VASc scores. SSE rates were modelled for various past and future AC scenarios. A total of 107 137 AF patients were evaluated (mean age = 74 years, 45% female). AF prevalence increased from 1.75 to 2.22% (*P*-value <0.001). SSE hospitalizations decreased by 18% (2.34–1.92%, *P*-value <0.001). Increased AC coverage from 50 to 70% was associated with a 37% lower SSE rate, after adjustment for individual time-dependent CHA_2DS_2VASc scores. The observed AC increase accounted for approximately 80 fewer SSE hospitalizations per 100 000/year. If 90% AC coverage had been achieved since 2012, an estimated 279 SSE per 100 000/year may have been prevented. Our model also predicts that improving AC coverage to 90% over the next 9 years could reduce annual SSE rates by 9%.

Conclusion We quantified the relationship between observed AC coverage, estimating the potential impact of variation in the timing of large-scale implementation. These data emphasize the importance of timely implementation and the considerable opportunity to improve clinical outcomes in the Wales-AF population.

* Corresponding author. Email: j.p.j.halcox@swansea.ac.uk
† These authors contributed equally.
‡ Joint senior authors.

Graphical Abstract



Keywords Atrial fibrillation • Stroke and systemic embolism • Anticoagulation • Electronic health records

Introduction

Atrial fibrillation (AF) is a major, yet treatable risk factor for stroke and systemic embolism (SSE), and is implicated in 20–30% of all strokes.[1] Anticoagulation (AC) significantly reduces the risk of stroke,[2] while antiplatelet therapy (AP) is no longer recommended.[3] However, implementation of these guidelines recommendations has been low in many populations.[4–6]

Suboptimal rates of AC coupled with an increasing prevalence of AF are a public health concern.[7–12] To reduce the risk of SSE in patients with AF, guidelines recommend appropriate AC in patients with a moderate to high risk of stroke ($CHA_2DS_2VASc \geq 2$).[13–17] In recent years, there has been an improvement in the rate of AC prescribing among patients with AF, yet many patients remain untreated with AC despite its evident effectiveness in preventing adverse thromboembolic events.[18,19] Multiple studies using electronic health records (EHRs) have reported on the changes in AC prescribing patterns.[20–22] The use of linked EHR data capturing changes in AF prevalence, adoption of guideline recommended AC prescribing, and the change in hospitalization rate for SSE at the population-level can add to the existing knowledge by providing insights into the adoption of the clinical guidelines in routine practice and the impact on SSE outcomes.

Previous studies using aggregated datasets have shown an increase in AF prevalence and a reduction in hospitalizations for stroke associated with an increase in AC prescribing.[22] But no specific analyses have been conducted using longitudinal population-scale, individual-level linked data to examine relationships between the rate of implementation and the overall extent of coverage of (guideline recommended) AC prescribing and systemic embolism (SE) or combined SSE outcomes, allowing estimation of their overall impact at a population-level. Furthermore, there is a complex interplay between changes in AF prevalence, increasing AC prescribing, and individual-level stroke risk,

which all influence the resulting hospitalization rate for SSE in large populations.

In this study using linked EHR data sources, we aimed to (i) quantify the impact of the rate of implementation of AC on hospitalizations for SSE, accounting for changes in AF prevalence, clinical risk factors, and time; (ii) model the impact of counterfactual scenarios of greater coverage of AC guidelines in the past and provide projections of future benefits of meeting therapeutic guidelines based on varying AC coverage in AF patients in a large population, over the coming years.

Method

We conducted a retrospective observational study using individual-level population-scale linked primary and secondary care EHR data over 7 years. Our longitudinal cohort consisted of 107 137 AF patients (mean age = 74 and 45% female) followed up between 2012 and 2018. Changes in antithrombotic prescriptions, stroke risk score (CHA_2DS_2-VASc)[13] and hospitalizations for SSE were recorded between 1 January 2012 and 30 December 2018. A Markov model was used to estimate hazard ratios (HRs) for hospitalizations, adjusting for time-dependent covariates, and to simulate scenarios of expected hospitalization rates under counterfactual past AC coverage and future implementation levels of therapeutic guidelines.

Inclusion criteria and data sources

Access to anonymized individual-level population-scale primary and secondary care EHR data sources was available within the Secure Anonymised Information Linkage (SAIL) Databank—the Trusted Research Environment (TRE) for Wales UK.[23,24] SAIL Databank holds an array of longitudinal anonymized, individual-level, population-scale data, including Welsh Longitudinal General Practice (WLGP),[25] which is coded using clinical Read codes and Patient Episode Dataset for Wales (PEDW),[26] which is coded using International Classification of Disease version 10 (ICD-10). We identified AF cases as a group of individuals aged ≥18 years at AF diagnosis date[27,28] (see Supplementary material online, *Tables S1 and S2* for diagnostic and drug codes). Patients with a diagnosis of AF recorded in WLGP from 1 January 2000 (records are less complete prior to this date) who were alive on 1 January 2012 were included as prevalent cases, while those with a new diagnosis of AF during the study period were included as incident cases. PEDW data contains records of all hospitalizations within NHS Wales secondary care organizations, SSE outcome events were identified from PEDW (see Supplementary material online, *Table S3* holds ICD-10 codes used to identify outcome events). All patients were followed until 31 December 2018. Censoring occurred at the date of death or loss to follow-up within the primary care record (defined by end date of registration with the general practice). Patients with less than 90 days of data coverage during the follow-up period were excluded from the study (see Supplementary material online, *Info S1*, *Table S4*, and *Figure S1*).

Antithrombotic therapy

Individual prescriptions for antithrombotic therapy (AT) (including AC and AP) were identified from the primary care data (see Supplementary material online, *Table S2* holds a list of Read codes used to extract relevant prescriptions). In each quarter (3-months) of the study period, patients were identified as being prescribed AC [including vitamin K antagonists (VKA) or direct oral anticoagulation (DOAC)], AP (including aspirin, $P2Y_{12}$ antagonist therapy, and/or dipyridamole), or no AT therapy. Patients prescribed both AP and AC within a quarter were assigned as AC. Individual prescriptions for specific AT were reassessed continuously during the study period.

Medical history and demographic information

Primary and secondary care EHR data were used to identify comorbidities and risk factors for stroke captured continuously during the study period. The presence of heart failure, hypertension, vascular disease (defined as prior MI, peripheral vascular disease, or aortic plaque), diabetes mellitus, ischaemic stroke [including transient ischaemic attack (TIA)], sex, and age were used to calculate the individual CHA_2DS_2-VASc score at entry into the study and was updated on the date of new diagnosis of a relevant risk factor or increase in age category (see Supplementary material online, *Tables S5 and S6* for diagnostic Read and ICD10 codes used in CHA_2DS_2-VASc and Supplementary material online, *Figure S3* for details of datasets used).

Outcome events: stroke and systemic embolism

Hospitalizations for (i) stroke (ischaemic and/or haemorrhagic) and systemic embolism (SSE), (ii) stroke and (iii) non-stroke systemic embolism (SE) during follow-up period were recorded every quarter (see Supplementary material online, *Table S3* for diagnostic codes). Hospital admissions for SSE spanning a 3-month length interval were only recorded for the first quarter in which the index hospitalization occurred (see Supplementary material online, *Info S2* and *Figure S2* for details).

Ethical approval and information governance

The data used in this study are available in the SAIL Databank at Swansea University, Swansea, UK. All proposals to use SAIL data are subject to review by an independent Information Governance Review Panel (IGRP). Before any data can be accessed, approval must be given by the IGRP. The IGRP gives careful consideration to each project to ensure proper and appropriate use of SAIL data. When access has been approved, it is gained through a privacy-protecting safe haven and remote access system referred to as the SAIL Gateway. SAIL has established an application process to be followed by anyone who would like to access data via SAIL (https://www.saildatabank.com/application-process). This study has been approved by the IGRP as project 0866.

Statistical analyses

Observational data

The numbers of patients with AF, their clinical (stroke risk factors and AT prescriptions) and demographic characteristics were summarized annually throughout the study period. The prevalence and incidence of AF within the population was calculated in each quarter [the denominator being the number of patients registered with a primary care general practitioner (GP) on the 1st January of each year]. Prescribing of AT within the AF cohort was also assessed quarterly. The absolute numbers of patients and proportion of patients with AF hospitalized for (i) SSE, (ii) stroke, and (iii) non-stroke systemic embolism was reported quarterly (proportion calculated from the quarterly AF prevalence). Absolute differences and 95% confidence intervals (CIs) were reported between the mean of the first 12-month period and the last 12-month period. We used logistic regression models to assess whether an observed change over time in the proportion of patients with AF and their clinical and demographic characteristics were statistically significant.

Estimating the effect of AC and CHA_2DS_2VASc on SSE rates

We used a multi-state Markov model with four progressive disease states: AF (state 1), one hospitalization for SSE (state 2), any subsequent hospitalization for SSE (state 3), and death (state 4)[29] (*Figure 1*). Individuals enter the cohort either at a prevalent state, at the start of 2012, or as an incident diagnosis of AF incident diagnosis of AF arising during the course of the simulation (state 1). From this point, transitions are possible to state 2 (first SSE hospitalization) or the absorbing state 4 (death). From state 2 (first SSE hospitalization), we considered possible transitions to state 3 (any further SSE hospitalization) or death. From state 3, we considered the transition rate to state 4 (death). Patients with pre-existing conditions such as prior SSE were allowed to enter the model at state 2. The transition rates were estimated for time-dependent covariates representing individual AC and CHA_2DS_2-VASc level. Although the model did not include the risk factors individually, the CHA_2DS_2-VASc score is a well-validated and internationally recommended predictor of SSE risk[13,30] comprising a combination of key SSE risk indicators: heart failure, hypertension, vascular disease, diabetes mellitus, ischaemic stroke, sex, and age. The model is described in detail in *Figure 1*.

The four-state Markov model was fitted in R (version 5.3) using the msm package,[29] which is specifically designed for maximum likelihood estimate of transition rates from interval sampled data, appropriate here due to our 3-month updating of the covariate status of individuals. Exact event dates were used for SSE and death. We estimated HRs and 95% CI for each covariate, for each possible transition pathway in the model. Hence, we calculated the effect of AC prescribing on SSE event rates, adjusted for the CHA_2DS_2-VASc score, and accounted for other state changes/the competing risk of death in the cohort. This approach allowed us to use multiple changes in prescribing and risk for each individual longitudinally. We also included a year covariate in the model to adjust for any additional time trends unaccounted by AC and CHA_2DS_2-VASc score, likely related to (unspecified) treatment or management changes.

Simulating the impact of different AC strategies

Given the estimated transition rates, we used the Markov model framework to simulate a population subject to different hypothetical anticoagulation scenarios, and how this would impact the number of SSE events. We explored four different scenarios over the period 2012–18, using a reference scenario (a) in which the prescribing of AC increased from 50 to 70% in a linear manner (approximately the observed change in AC in our cohort) during that period, and using the observed CHA_2DS_2-VASc levels. In comparison, we investigated the following counterfactual past AC strategies: (b) only 50% of the cohort had received AC throughout the study period, (c) a constant 70% of the population had prescribed AC throughout the study period, and (d) AC prescription had started at the higher level of 70% in 2012 and had risen linearly to 90% by 2018. Model validation was assessed by goodness-of-fit to the observed trends of SSE and stroke rates over the period 2012–18. The output of the model provided a close fit to the observed trends as can be seen using the 'reference scenario' of a gradual increase from 50 to 70% AC prescribing (details in Supplementary material online, *Tables*). We chose the '50–70' scenario as a simplified case, for clarity. If the precise AC prescribing rates were used each year to generate a model output (rather than the approximate linear increase from 50 to 70%), we found that we obtained an even closer fit to the data each year, hence the model was able to closely reproduce observed trends.

Similarly, we forecasted scenarios for the next 9-year period on three different scenarios, assuming (e) continuing the level of AC observed in 2018 of 70%, (f) a gradual (linear) improvement from 70% in 2018 to 90% in 2027, (g) an immediate and sustained improvement with a constant AC level at 90%. For future scenarios, we fixed the size and CHA_2DS_2-VASc risk status of the population at the levels observed in 2018, carrying this value forward unchanged for the future modelling period. In each scenario, we calculated the total number of expected SSE events and deaths per 100 000 AF population. Since AF prevalence is increasing, we also calculated event numbers relevant to the absolute cohort population size (or Wales population) using an extrapolation of the AF population increase (and an adjustment for the SAIL Databank coverage, which is approximately 80% of the Welsh population). All code and data are openly available on request.

Sensitivity analyses

We conducted a series of analyses to evaluate the sensitivity of the observed trends, and the Markov model was developed based on the observational data: (I) all rates were calculated both per quarter and as annual rates and (II) models were fitted on a subset of the population under 80 years, to evaluate the effect of age-related morbidities (see Supplementary material online, *Tables S8–S11*). The sensitivity of the simulated model was evaluated based on a scenario which matched the observed counts in the population (a gradual increase in AC rate from 50 to 70% over the 7 years observational period). We also compared the two models with and without the time (see Supplementary material online, *Tables S8–S10*).

Results

A total of 107 137 patients with AF, comprising 435 038 patient-years follow-up were included in the analyses, of whom 52 650 entered the study as prevalent cases (diagnosis made before 2012) and 54 487 who acquired a new diagnosis of AF between 2012 and 2018 (*Figure 2*). The mean follow-up time during the study was 4.1 years.

The number of patients with AF increased from 55 631 to 71 673 between the first quarter of 2012 and the last quarter of 2018; an increase in the prevalence of AF from 1.75 to 2.22%; absolute difference of 0.47%, 95% CI 0.43–0.68. In the subset of population with a CHA_2DS_2-VASc ≥ 2, AF prevalence increased from 1.46 to 1.89%; absolute difference of 0.43%, 95% CI 0.42–0.44 between 2012 and 2018. There were on average 7784 new AF cases per year across the study period, with an annual incidence in the population increasing from 0.23 to 0.26% from 2012 to 2018 ($P < 0.001$) (see Supplementary material online, *Table S7* for annual incidence).

The mean age of the cohort increased from 74.0 SD $\pm$ 12.10 to 74.9 $\pm$ 12.01 ($P < 0.001$), the proportion of females decreased from 45 to 43% ($P < 0.001$), and the mean CHA_2DS_2-VASc score increased modestly from 3.21 to 3.31 ($P < 0.001$; *Table 1*).

Temporal trends

Antithrombotic prescribing

Across the study period, the proportion of patients with AF prescribed AC increased from 48.5% in 2012 to 66.1% in 2018, representing an increase of 17.6%, 95% CI 17.5–17.7, $P < 0.001$. The average rate of increase of AC per year was 2.5%. Prescribing of AP therapy decreased from 27.3 to 8.1%, representing a decrease of 19.2%, 95% CI 19.1–19.4, $P < 0.001$. The average rate of decrease of AP per year was 2.7% (*Figure 3*). The proportion of patients not prescribed any AT increased marginally from 24.2 to 25.8%, representing an increase of 1.6%, 95% CI 1.5–1.7, $P < 0.05$.

In patients with a CHA_2DS_2-VASc ≥ 2, the proportion prescribed AC increased from 52.0 to 70.4%, representing an increase of 18.5%, 95% CI 18.3–18.6, $P < 0.05$. The average rate of increase of AC per year was 2.6%. The proportion of patients' prescribed AP therapy among those with CHA_2DS_2-VASc ≥ 2 decreased from 27.6 to 8.2%, representing a decrease of 19.4%, 95% CI 17.9–20.8, $P < 0.05$. The average rate of decrease in AP was 2.8%. The proportion receiving

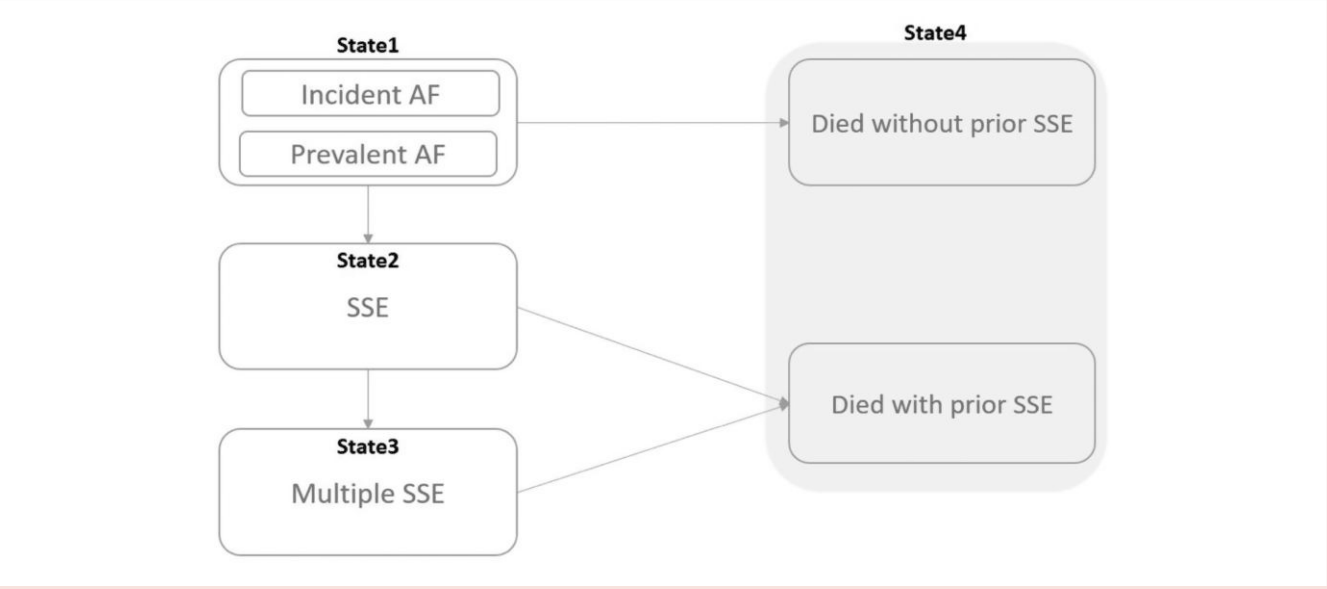


Figure 1 Multi-state Markov model: overview of states and possible transitions considered in this analysis.

no AT increased from 20.4 to 21.3%, representing an increase of 0.9%, 95% CI 0.7–1.1, $P < 0.05$.

Among those prescribed AC, the mean CHA_2DS_2-VASc score increased from 3.4 to 3.6 ($P < 0.001$) and among those not prescribed AC, the mean CHA_2DS_2-VASc score decreased from 3.00 to 2.96 (see Supplementary material online, *Figures S4 and S5*).

SSE hospitalizations

Across the study period, there were a total of 9666 hospitalizations for SSE among 8992 patients with AF. In 2012, there were 1300 hospitalizations for SSE among 1215 patients increasing to 1482 hospitalizations among 1377 patients in 2018. The annual rate of SSE hospitalizations in the AF population decreased from 2.3 to 2.1% between 2012 and 2018 (absolute difference = 0.20, 95% CI 0.02–3.7, $P < 0.05$).

Stroke hospitalizations

There were a total of 8562 hospitalizations for stroke among 8005 patients with AF. In 2012, there were 1160 hospitalizations for stroke among 1087 patients, increasing to 1301 hospitalizations record among 1091 patients in 2018. The rate of stroke hospitalizations in the AF population decreased from 2.1 to 1.8% between 2012 and 2018 (absolute difference = 0.3, 95% CI 0.02–3.7, $P < 0.05$).

Non-stroke systemic embolism (SE)

There were a total of 1144 hospitalizations for non-stroke SE among 1049 patients with AF. In 2012, there were 143 hospitalizations for SE among 133 patients, increasing to 191 hospitalizations recorded among 172 patients in 2018. The rate of non-stroke SE hospitalizations for the population of Wales increased minimally from 0.26 to 0.27% between 2012 and 2018 (absolute difference = 0.01, 95% CI 0.001–0.012, $P < 0.05$).

Estimation of the effect of AC and CHA_2DS_2VASc on SSE rates

Multi-state Markov modeling estimated that the increased use of AC was associated with a 37% lower rate of SSE (HR = 0.63, 95% CI 0.60–0.66, $P < 0.001$), after adjusting for CHA_2DS_2VASc risk score and year. As expected, a one-point increase in CHA_2DS_2VASc score was associated with a greater likelihood of SSE (HR = 2.16, 95% CI 2.13–2.18) and death (HR = 1.44, 95% CI 1.43–1.45) in AF patients. Following an SSE event, each point increase in CHA_2DS_2VASc was associated with a 7% higher chance of recurrent SSE (HR = 1.07, 95% CI 1.04–1.09) and 16% higher chance of death (HR = 1.16, 95% CI 1.13–1.18).

Time trends in the model suggested a significant additional improvement in overall SSE outcome rates over the study period, adjusted for AC and CHA_2DS_2VASc (see Supplementary material online, *Table S8*). We also found that AC was associated with a lower likelihood of death (*Table 2*) (For details, see figures and tables provided in Supplementary material online, *Info S3*). Three separate models were fitted using either stroke and systemic embolism, stroke only, or systemic embolism only as the hospitalization events in the model (see Supplementary material online, *Info S3*).

Simulating the impact of different AC strategies

Our reference prescribing scenario for modeling was a 50–70% linear increase in the proportion of AF patients prescribed AC from 2012 to 2018, which approximates the changes in prescribing coverage that we observed in the All-Wales AF cohort. Over the observation period (2012–18), we estimated that the reference prescribing scenario was associated with an average of 81 per 100 000 fewer SSE hospitalizations per year in the AF population, in comparison with a counterfactual scenario where the AC coverage had remained unchanged, at 50% throughout (*Figure 4*). However, if 70% AC had been introduced (and maintained) from 2012, we estimated that an additional 97 SSE might have been prevented per year (per 100 000 AF). Furthermore, if AC coverage of 90% had been achieved from 2012, then we estimated that 279 SSE per year (per 100 000 AF patients) may have been prevented, in comparison with the representative reference scenario (see Supplementary material online, *Info S3* for modeled data for Stroke and Systemic Embolism alone).

Extending the scenarios into the future (up until 2027), we specifically focused on modelling the potential impact of AC, considering a

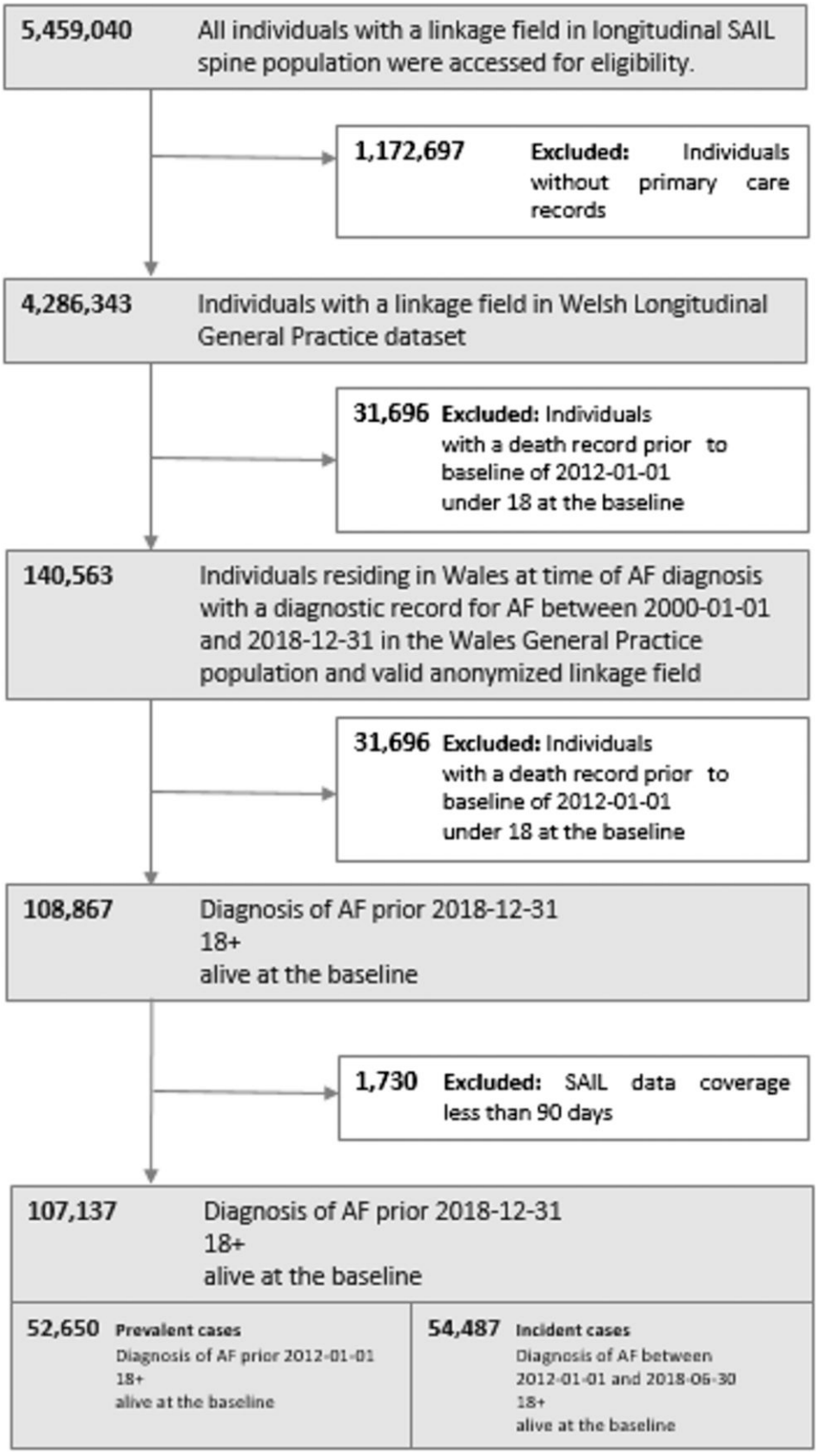


Figure 2 Summary of record extraction at each stage of study.

Table 1 AF cohort characteristics and risk factors by year

Characteristics	Years							*P*-value[a]
	2012	2013	2014	2015	2016	2017	2018	
n	56 727	59 374	62 251	64 666	67 666	70 171	72 715	
Age mean (SD)	73.98 (12.10)	74.11 (12.09)	74.28 (12.06)	74.43 (12.03)	74.58 (12.02)	74.74 (12.00)	74.91 (12.01)	<0.001
CHA_2DS_2VASc mean (SD)	3.21 (1.70)	3.23 (1.70)	3.26 (1.70)	3.28 (1.70)	3.29 (1.71)	3.30 (1.71)	3.31 (1.71)	<0.001
	%	%	%	%	%	%	%	
Age 18–65	21.7	21.2	20.3	20.1	19.8	19.3	19.1	<0.001
65–74	27.7	27.9	28.5	28.9	28.9	29.0	29.0	<0.001
75+	50.6	50.9	51.2	50.9	51.3	51.6	52.0	<0.001
Female	45.0	44.6	44.3	43.7	43.4	43.1	42.7	0.0754
Anticoagulant	49.3	51.5	55.3	59.1	62.3	65.1	66.8	<0.001
Antiplatelet	26.6	24.3	20.0	15.2	11.8	9.3	7.3	<0.001
Diabetes	21.0	21.5	22.1	22.7	23.4	23.6	23.8	<0.001
Vascular disease	31.0	31.1	31.1	31.0	30.9	30.7	30.6	0.0556
Stroke	8.3	8.5	8.8	9.0	9.2	9.3	9.3	<0.002
Hypertension	49.9	50.4	50.9	51.3	51.8	52.2	52.7	<0.001
Heart failure	23.2	23.4	23.8	23.8	23.8	23.9	23.8	<0.001

For each year, the presented population is the prevalent AF population at the end of the year.
AF, atrial fibrillation.
[a]All presented *P*-values are calculated from a logistic regression model fitted on the individual-level data with data points = *n*.

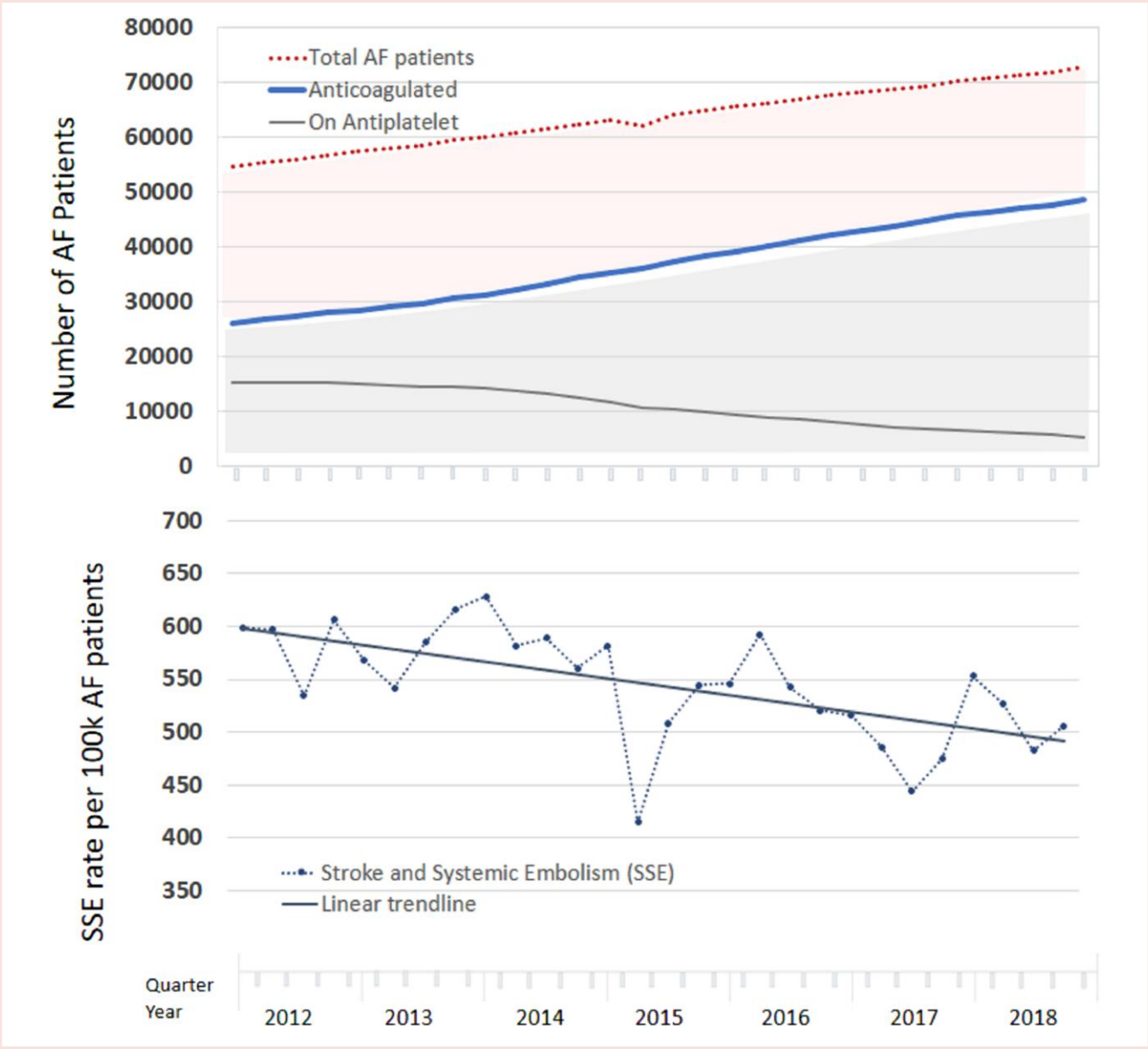


Figure 3 Top panel: trends in SSE rates per 100 000 AF patients in the study cohort. Bottom panel: quarterly trend of AF and AC in the cohort. Shaded regions illustrate the relative prevalence of AC in the (increasing) AF population (see Supplementary material online, *Figure S4* for SE and ST outcome events). AC, anticoagulation; AF, atrial fibrillation; SE, systemic embolism; SSE, stroke and systemic embolism.

stable distribution of CHA_2DS_2VASc score over time. If AC coverage remained stable at 70% (reference scenario), we would expect 1610 SSE per 100 000 AF patients per year (similar to observed outcomes in the cohort during 2018). This would represent an estimated 140 fewer SSE per 100 000 patients per year compared with a stable 50% AC scenario. If AC coverage were to increase to 90%, we estimate that this would be associated with a further reduction of 150 SSE per 100 000 patients per year vs. a stable 70% coverage scenario; representing a 9% lower rate of SSE in the AF population (see Supplementary material online, *Tables S12–S17* for full tables of scenario output).

We also estimated how these predicted changes in rates of SSE might translate into the changes in absolute numbers of SSE events in the population of Wales. We extrapolated a 4% annual increase of the size of the AF per year in our projection, to be consistent with the observed annual increase in AF patient numbers in the real-world population study. If future AC coverage remained stable at 70% (reference scenario), we would expect to observe a total of 12 467 SSE events in AF patients in Wales between 2019 and 2027. This would be 1084 fewer SSE events compared with stable 50% AC scenario; representing 8% lower rate of SSE in Wales if AC coverage had not improved. If AC coverage could be increased gradually from 70 to 90% over the same period, we would expect 774 fewer SSE; representing a 6% lower rate of SSE in the AF population in Wales. However, if AC coverage were increased immediately to 90% from 2019 onwards, we estimate that this would be associated with a further reduction of 1162 SSE; representing a 10% lower rate of SSE in those with AF in Wales (see Supplementary material online, *Tables S12–S17* for full tables of scenario output).

Table 2 Estimated hazard ratios for events, adjusted for CHA_2DS_2VASc, anticoagulation, and year, derived from multi-state Markov model

State transition	Hazard ratio for anticoagulation compared with no anticoagulation (95% CI)	Hazard ratio for one unit increase in CHA_2DS_2VASc score (95% CI)
AF-SSE	0.63 (0.60–0.66)	2.16 (2.13–2.18)
AF-Death	0.28 (0.27–0.29)	1.44 (1.43–1.45)
SSE-Multiple SSE	0.42 (0.39–0.45)	1.07 (1.04–1.09)
SSE-Death	0.20 (0.19–0.22)	1.16 (1.13–1.18)
Multiple SSE-Death	0.24 (0.21–0.27)	1.18 (1.14–1.23)

AF, atrial fibrillation; SSE, stroke and systemic embolism; CI, confidence interval.

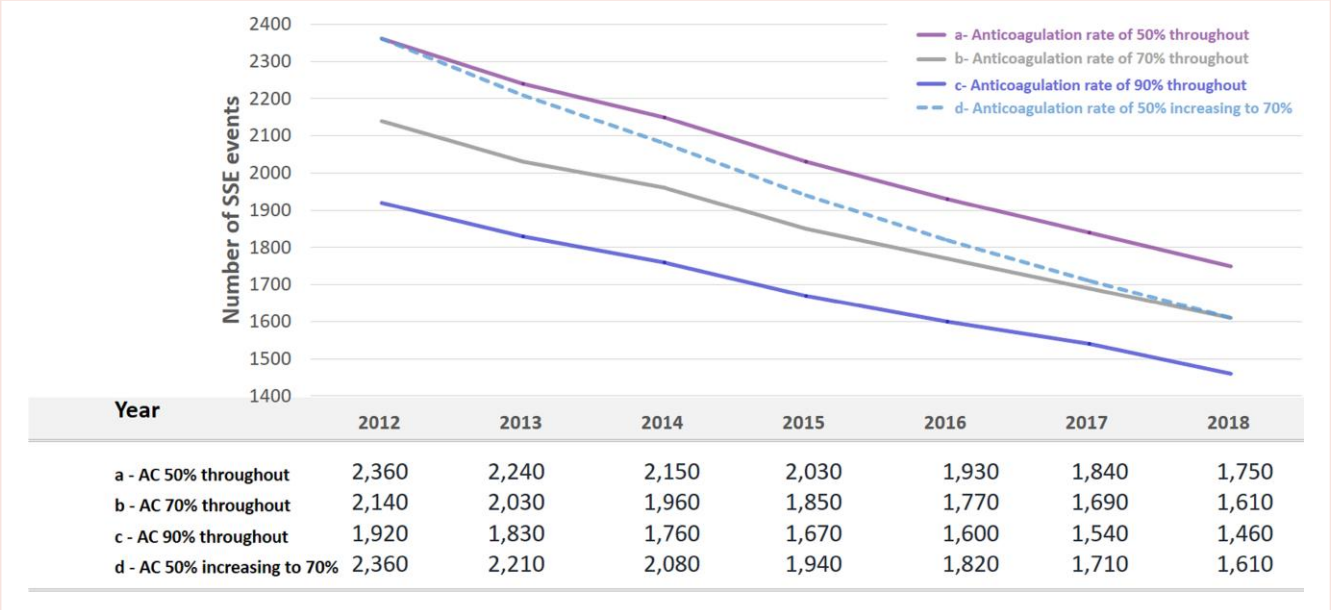
Discussion

To our knowledge, this is the first real-world population-scale study that has examined changes in the prevalence of AF, clinical characteristics, antithrombotic prescribing, and hospitalizations for both stroke and systemic embolism for patients at an individual-level across multiple EHR data sources. We observed a 26% increase in the prevalence of AF and a small increase in associated CHA_2DS_2VASc risk in this population between 2012 and 2018. We also observed an increase in the AF population AC coverage from 50 to 70% and a 15% reduction in the rate of hospitalization for SSE over this period.

It is well known that the AC improves outcomes in AF patients and the European Society of Cardiology guidelines for AF management, published in 2012,[30] recommended OAC in preference to AP therapy in (most) patients with a CHA_2DS_2VASc score ≥1. However, the direct impact of these recommendations on clinical outcomes, with regard to the level and rate of implementation of AC coverage at a population level has not been demonstrated in a large, real-world study. We, therefore, undertook this study to determine the changing trends in the size and thromboembolic risk (CHA_2DS_2VASc risk factors) of the AF population, the level of AC coverage and SSE events in a large population from 2012 to shortly before the COVID pandemic. Our key questions given the changing demographic of this population being: whether such guidelines are met, and what was the consequences over time of unmet therapeutic need which we measured by the rate of SSE hospitalization.[31,32]

As expected, we observed that the increasing proportion of AF patients prescribed AC was associated with a decrease in hospitalization rate for SSE, despite the increasing mean CHA_2DS_2VASc score of the AF population over the period of assessment. Although these are favourable outcomes, with coverage in line with other previous studies, the level and rate of increase in coverage is far from ideal.[15,33] Our model confirmed a very good fit with the observed outcomes between 2012 and 2018 providing us with the confidence that the simulated outcomes would be representative of clinical events in the AF population. Our model shows the expected magnitude of the benefit that might have been observed if the increase in coverage had been made more rapidly and extensively across the population. Furthermore, our model(s) allowed us to estimate the potential population impact of future changes in the level of AC coverage and rate of implementation, from the current starting point in our population. Unsurprisingly the quicker and more comprehensively these improvements can be implemented, the greater the impact on outcomes, illustrated by our estimate that almost 400 more SSE events in AF patients might be prevented if AC coverage could be increased to 90% immediately, compared with a gradual increase in coverage to 90% over the subsequent 9 years. This is a conservative estimate, as it assumes there will be no increase in the CHA_2DS_2-VASc score in the population.

Our national longitudinal study of anonymized population-scale individual-level data provides new and original knowledge on temporal trends in the increased prevalence of AF and associations between AC, CHA_2DS_2VASc risk score and the falling incidence of stroke and



Year	2012	2013	2014	2015	2016	2017	2018
a - AC 50% throughout	2,360	2,240	2,150	2,030	1,930	1,840	1,750
b - AC 70% throughout	2,140	2,030	1,960	1,850	1,770	1,690	1,610
c - AC 90% throughout	1,920	1,830	1,760	1,670	1,600	1,540	1,460
d - AC 50% increasing to 70%	2,360	2,210	2,080	1,940	1,820	1,710	1,610

Figure 4 Estimated stroke and systemic embolism (SSE) rates per 100 000 based on four anticoagulation (AC) coverage scenarios: (a) AC rate of 50% at the start of 2012 staying stable at 50% till the end; (b) AC rate of 70% at the start of 2012 staying stable at 70% till the end; (c) AC rate of 90% at the start of 2012 staying stable at 90% till the end; (d) AC rate of 50% at 2012 gradually increasing to 70% by the end.

systemic embolism, in Wales, UK. The unique data linkage within the TRE enables us to track patients from the point of AF diagnosis to any prescribed medication and monitor for this population any incident hospitalization for Stroke and Systemic Embolism (SSE), adding to the existing evidence based on aggregated level data only.[22] We were limited to those patients who have had a coded diagnosis of AF in their primary care records; hence, the ascertainment of AF cases as well as the outcomes are highly dependent on what is recorded in the datasets. However, these recorded diagnoses represent those considered by the responsible clinicians for the care of these patients. Notably, the SAIL Databank team performs standard quality assurance steps on all data received to SAIL to check the consistency of data flows over time and ensure that only data approved for project use is provisioned and accessible within the TRE.

Although all secondary care hospitals in Wales provide data to SAIL Databank, our data may slightly underestimate the effect size due to only 80% of primary care practices contributing data to SAIL Databank at the time of this study.

In keeping with many previous studies,[22,31,34,35] adverse outcomes were assessed from secondary care data only. Therefore, any SSE events not resulting in hospitalization managed in a different care setting or if the patient died prior to hospitalization will not have been recorded. This is likely to underestimate the true benefit of SSE reduction with AC. However, to our knowledge, there are no linkable data held in the SAIL Databank that could permit further exploration of this issue.

We observed a reduction in hospitalization rates for SSE during the study period, independent of changes to CHA_2DS_2-VASc score and antithrombotic prescribing. There are a number of possible explanations for this observation, including the improvement of patient pathways that may result in better management of risk factors and the earlier provision of AC. We acknowledge that although prescriptions for AT were evaluated, it was not possible to determine whether these medications were actually dispensed or taken as intended. Furthermore, changing patterns of other unrecorded comorbidities, the prescribing of other prognostically relevant medicines and behaviours may also have influenced outcomes. However, it was beyond the scope of this study to evaluate these issues. Nonetheless, despite these caveats, the output from our model provided a close estimate of the observed outcomes.

Our simulation analyses include adjustment for CHA_2DS_2VASc score and assumes that the risk-benefit balance of anticoagulating patients who are currently not receiving any AC is similar to those who are already anticoagulated. However, we recognize that some patients may not be anticoagulated due to contraindications and/or other clinical issues which we could not explore in this study. Although we cannot recommend wider generalization of these simulated findings, we believe that they provide meaningful and important insights into the potential clinical benefit from a more timely implementation of evidence based treatment at a population level.

There are a number of additional factors that may have contributed to our observation of improving outcomes in this population. These include the improvement of patient pathways as well as the 2012 updates of the European AF guidelines that may result in more effective opportunistic detection of AF, better management of cardiovascular risk factors and comorbidities in addition to the earlier provision of AC.

This study was conducted in the Welsh NHS, where healthcare is free at the point of care, including the provision of medicine, this should be considered when comparing the results of this study to other healthcare systems where affordability may influence access to treatment and outcomes.

Conclusion

Although the beneficial impact of AC in the reduction of thromboembolic risk in AF patients has been clearly demonstrated in clinical trials, the overall level of benefit 'at scale' in a real-world cohort has not previously been fully characterized.[36] In this study, we have quantified the relationship between increasing AC coverage and falling rates of SSE and mortality and provided a model framework to estimate the past and future impact of differing scenarios of population AC coverage. These data emphasize the missed opportunities of delays in meeting therapeutic targets for a simple, inexpensive pharmaceutical intervention, and the need for continued efforts to improve population AC coverage as quickly and comprehensively as possible.

Data availability

The data sources used in this study are available in the SAIL Databank at Swansea University, Swansea, UK, but as restrictions apply, they are not publicly available. All proposals to use SAIL data are subject to review by an independent Information Governance Review Panel (IGRP). Before any data can be accessed, approval must be given by the IGRP. The IGRP considers each project to ensure proper and appropriate use of SAIL data. When access has been granted, it is gained through a privacy protecting trusted research environment and remote access system, referred to as the SAIL Gateway. SAIL has established an application process to be followed by anyone who would like to access data via SAIL at https://www.saildatabank.com/application-process.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Authors' contributions

J.H. generated the original proposal of work, and all authors have been involved in generating the study protocol and statistical analyses plan. F.T. conducted data curation and analyses overseen by M.G. and O.B. F.T. and D.H. jointly generated the report of outcomes and drafted the article. J.H., R.A.L., A.A., M.G., and O.B. reviewed the data and current manuscript at multiple stages. All authors confirm that the presented results in the manuscript are an accurate representation of research. F.T. and D.H. affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; and that no important aspects of the study have been omitted.

Acknowledgements

We would like to acknowledge that all of this work would not have been possible without the contribution of the public and patients. Our applications submitted to SAIL Databank have been reviewed by the independent Information Governance Review Panel, which comprises the public panel members who review applications and provide feedback that informs ongoing and future research and contributes to the cogeneration of research ideas.

Funding

This work was supported by Health Data Research UK [HDR-9007], which receives its funding from the UK Medical Research Council, Engineering and Physical Sciences Research Council, Economic and Social Research Council, Department of Health and Social Care (England), Chief Scientist Office of the Scottish Government Health and Social Care Directorates, Health and Social Care Research and Development Division (Welsh Government), Public Health Agency (Northern Ireland), British Heart Foundation (BHF), and the Wellcome Trust; and Administrative Data Research UK which is funded by the Economic and Social Research Council [grant ES/S007393/1].

Conflict of interest: All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/disclosure-of-interest/ and declare: core supported funding for the current study from Health Data Research UK covered in the Role of the funding section. JPH has received personal fees from Bristol Myers Squibb, Pfizer, Boehringer Ingelheim, and Bayer outside the submitted work and received research and research grants from British Heart Foundation, Welsh Government, Bristol Myers Squibb/Pfizer Alliance, all noted as not being directly related to this manuscript. DH has recieved personal fees from Bristol Myers Squibb, Pfizer, outside the submitted work.

APPENDIX

Abbreviated term	Description
AC	Anticoagulation
AF	Atrial fibrillation
AP	Antiplatelet therapy
AT	Antithrombotic
CHA_2DS_2-VASc	Congestive heart failure, Hypertension, Age (65–74), Diabetes, Stroke history, Vascular disease, Age (75+), Sex
CI	Confidence interval
DOAC	Direct oral anticoagulation
GP	General Practice
EHR	Electronic health record
HR	Hazard ratios
ICD-10	International Classification of Disease – 10th revision
PEDW	Patient Episode Dataset for Wales
SAIL	Secure Anonymised Information Linkage
SE	Systemic embolism
SSE	Stroke and systemic embolism
TIA	Transient ischaemic attack
TRE	Trusted Research Environment
VKA	Vitamin K antagonists
WLGP	Welsh Longitudinal General Practice

References

1. Kirchhof Paulus, Benussi Stefano, Kotecha Dipak, Ahlsson Anders, Atar Dan, Casadei Barbara, Castella Manuel, Diener Hans-Christoph, Heidbuchel Hein, Hendriks Jeroen, Hindricks Gerhard, Manolis Antonis S, Oldgren Jonas, Popescu Bogdan Alexandru, Schotten Ulrich, Van Putte Bart, Vardas Panagiotis, Agewall Stefan, Camm John, Esquivias Gonzalo Baron, Budts Werner, Carerj Scipione, Casselman Filip, Coca Antonio, De Caterina Raffaele, Deftereos Spiridon, Dobrev Dobromir, Ferro José M, Filippatos Gerasimos, Fitzsimons Donna, Gorenek Bulent, Guenoun Maxine, Hohnloser Stefan H, Kolh Philippe, Lip Gregory YH, Manolis Athanasios, McMurray John, Ponikowski Piotr, Rosenhek Raphael, Ruschitzka Frank, Savelieva Irina, Sharma Sanjay, Suwalski Piotr, Tamargo Juan Luis, Taylor Clare J, Van Gelder Isabelle C, Voors Adriaan A, Windecker Stephan, Zamorano Jose Luis, Zeppenfeld Katja. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur J Cardio Thoracic Surg* 2016;**50**:e1–e88.
2. Asplund K. High prevalence of atrial fibrillation among patients with ischemic stroke. *Stroke* 2014;**45**:2599–2605.
3. NICE. Atrial fibrillation: diagnosis and management. 2021. https://www.nice.org.uk/guidance/ng196 (31 October 2022).
4. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GYH. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. *Am J Med* 2010;**123**:638–645.e4.
5. Camm A. John, on behalf of the Writing Committee of the Action for Stroke Prevention alliance, Pinto Fausto J, on behalf of the Writing Committee of the Action for Stroke Prevention alliance, Hankey Graeme J, on behalf of the Writing Committee of the Action for Stroke Prevention alliance, Andreotti Felicita, on behalf of the Writing Committee of the Action for Stroke Prevention alliance, Richard Hobbs FD, on behalf of the Writing Committee of the Action for Stroke Prevention alliance, on behalf of the Writing Committee of the Action for Stroke Prevention alliance, John Camm A, Pinto Fausto J, Hankey Graeme J, Andreotti Felicita, Richard Hobbs FD, Csiba László, de Freitas Gabriel R, Goto Shinya, Cantú Carlos, Gonzalez-Zuelgaray Jorge, Hacke Werner, Hu Han Hwa, Mantovani Lorenzo, Yoon Byung-Woo, Hu Dayi, Sim Kui-Hian. Non-vitamin K antagonist oral anticoagulants and atrial fibrillation guidelines in practice: barriers to and strategies for optimal implementation. *Europace* 2015;**17**:1007–1017.
6. Tagney J. Anticoagulation in atrial fibrillation: delayed implementation of evidence. *Br J Card Nurs* 2015;**10**:378–381.
7. Lip GYH, Brechin CM, Lane DA. The global burden of atrial fibrillation and stroke: a systematic review of the epidemiology of atrial fibrillation in regions outside North America and Europe. *Chest* 2012;**142**:1489–1498.
8. Patel NJ, Atti V, Mitrani RD, Viles-Gonzalez JF, Goldberger JJ. Global rising trends of atrial fibrillation: a major public health concern. *Heart* 2018;**104**:1989–1990.
9. Kishore A, Vail A, Majid A, Dawson J, Lees KR, Tyrrell PJ, Smith CJ. Detection of atrial fibrillation after ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. *Stroke* 2014;**45**:520–526.
10. Wang Thomas J, Larson Martin G, Levy Daniel, Vasan Ramachandran S, Leip Eric P, Wolf Philip A, D'Agostino Ralph B, Murabito Joanne M, Kannel William B, Benjamin Emelia J. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham heart study. *Circulation* 2003;**107**:2920–2925.
11. Colilla Susan, Crow Ann, Petkun William, Singer Daniel E, Simon Teresa, Liu Xianchen. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *Am J Cardiol* 2013;**112**:1142–1147.
12. Ball J, Carrington MJ, McMurray JJV, Stewart S. Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century. *Int J Cardiol* 2013;**167**:1807–1824.
13. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach. *Chest* 2010;**137**:263–272.
14. Gu J, Jia F, Feng P. [$CHADS_2$versus CHA_2DS_2-VASc scoring systems for predicting left atrial thrombus in patients with nonvalvular atrial fibrillation]. *Nan Fang Yi Ke Da Xue Xue Bao* 2014;**34**:1601–1605.
15. Hindricks Gerhard, Potpara Tatjana, Dagres Nikolaos, Arbelo Elena, Bax Jeroen J, Blomström-Lundqvist Carina, Boriani Giuseppe, Castella Manuel, Dan Gheorghe Andrei, Dilaveris Polychronis E, Fauchier Laurent, Filippatos Gerasimos, Kalman Jonathan M, La Meir Mark, Lane Deirdre A, Lebeau Jean Pierre, Lettino Maddalena, Lip Gregory YH, Pinto Fausto J, Neil Thomas G, Valgimigli Marco, Van Gelder Isabelle C, Van Putte Bart P, Watkins Caroline L. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2021;**42**:373–498.
16. NICE. Atrial fibrillation: quality standards. 2018. https://www.nice.org.uk/guidance/qs93 (31 October 2022).
17. January Craig T, Samuel Wann L, Alpert Joseph S, Calkins Hugh, Cigarroa Joaquin E, Cleveland Joseph C, Conti Jamie B, Ellinor Patrick T, Ezekowitz Michael D, Field Michael E, Murray Katherine T, Sacco Ralph L, Stevenson William G, Tchou Patrick J, Tracy Cynthia M, Yancy Clyde W. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014;**64**:e1–e76.
18. Lacoin Laure, Lumley Matthew, Ridha Essra, Pereira Marta, McDonald Laura, Ramagopalan Sreeram, Lefèvre Cinira, Evans David, Halcox Julian P. Evolving landscape of stroke prevention in atrial fibrillation within the UK between 2012 and 2016: a cross-sectional analysis study using CPRD. *BMJ Open* 2017;**7**:1–16.
19. Wu Jianhua, Alsaeed Eman S, Barrett James, Hall Marlous, Cowan Campbell, Gale Chris P. Prescription of oral anticoagulants and antiplatelets for stroke prophylaxis in atrial fibrillation: nationwide time series ecological analysis. *Europace* 2020;**22**:1311–1319.
20. Chen YC, Roebuck AE, Sami A, Ersin ÖH, Mirro MJ. The use of electronic personal health records to improve medication adherence and patient engagement: a randomized study of non-valvular atrial fibrillation patients. *J Innov Card Rhythm Manag* 2017;**8**:2804.
21. Curtis Helen J, MacKenna Brian, Walker Alex J, Croker Richard, Mehrkar Amir, Morton Caroline, Bacon Seb, Hickman George, Inglesby Peter, Bates Chris, Evans David, Ward Tom, Cockburn Jonathan, Davy Simon, Bhaskaran Krishnan, Schultze Anna, Rentsch Christopher T, Williamson Elizabeth, Hulme William, Tomlinson Laurie, Mathur Rohini, Drysdale Henry, Eggo Rosalind M, Wong Angel Yun, Forbes Harriet, Parry John, Hester Frank, Harper Sam, Douglas Ian, Smeeth Liam, Goldacre Ben.

OpenSAFELY: impact of national guidance on switching anticoagulant therapy during COVID-19 pandemic. *Open Heart* 2021;**8**:e001784.
22. Campbell Cowan J, Wu Jianhua, Hall Marlous, Orlowski Andi, West Robert M, Gale Chris P. A 10 year study of hospitalized atrial fibrillation-related stroke in England and its association with uptake of oral anticoagulation. *Eur Heart J* 2018;**39**:ehy411.
23. Lyons Ronan A, Jones Kerina H, John Gareth, Brooks Caroline J, Verplancke Jean Philippe, Ford David V, Brown Ginevra, Leake Ken. The SAIL databank: linking multiple health and social care datasets. *BMC Med Inform Decis Mak* 2009;**9**.
24. Ford David V, Jones Kerina H, Verplancke Jean Philippe, Lyons Ronan A, John Gareth, Brown Ginevra, Brooks Caroline J, Thompson Simon, Bodger Owen, Couch Tony, Leake Ken. The SAIL databank: building a national architecture for e-health research and evaluation. *BMC Health Serv Res* 2009;**9**:1–12.
25. Welsh Longitudinal General Practice Dataset (WLGP) - Welsh Primary Care. https://web.www.healthdatagateway.org/dataset/33fc3ffd-aa4c-4a16-a32f-0c900aaea3d2 (6 February 2022).
26. PEDW dataset in SAIL. https://saildatabank.com/saildata/sail-datasets/patient-episode-database-for-wales-pedw/ (7 August 2020).
27. WDSD. Welsh Demographic Service Dataset (WDSD) 2022. https://web.www.healthdatagateway.org/dataset/8a8a5e90-b0c6-4839-bcd2-c69e6e8dca6d (6 February 2022).
28. WLGP dataset in SAIL. https://saildatabank.com/saildata/sail-datasets/primary-care-gp-dataset/ (7 August 2020).
29. Jackson C. *Multi-state modelling with R: the msm package 1 Multi-state models 1.1 Introduction*: R Cran Library; 2019.
30. Camm A. John, Lip Gregory YH, De Caterina Raffaele, Savelieva Irene, Atar Dan, Hohnloser Stefan H, Hindricks Gerhard, Kirchhof Paulus, Bax Jeroen J, Baumgartner Helmut, Ceconi Claudio, Dean Veronica, Deaton Christi, Fagard Robert, Funck-Brentano Christian, Hasdai David, Hoes Arno, Knuuti Juhani, Kolh Philippe, McDonagh Theresa, Moulin Cyril, Popescu Bogdan A, Reiner Željko, Sechtem Udo, Sirnes Per Anton, Tendera Michal, Torbicki Adam, Vahanian Alec, Windecker Stephan, Vardas Panos, Al-Attar Nawwar, Alfieri Ottavio, Angelini Annalisa, Blömstrom-Lundqvist Carina, Colonna Paolo, De Sutter Johan, Ernst Sabine, Goette Andreas, Gorenek Bulent, Hatala Robert, Heidbüchel Hein, Heldal Magnus, Kristensen Steen Dalby, Le Heuzey Jean Yves, Mavrakis Hercules, Mont Lluís, Filardi Pasquale Perrone, Ponikowski Piotr, Prendergast Bernard, Rutten Frans H, Schotten Ulrich, Van Gelder Isabelle C, Verheugt Freek WA. 2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Europace* 2012;**14**:1385–1413.
31. Yiin Gabriel SC, Howard Dominic PJ, Paul Nicola LM, Li Linxin, Mehta Ziyah, Rothwell Peter M. Recent time trends in incidence, outcome and premorbid treatment of atrial fibrillation-related stroke and other embolic vascular events: a population-based study. *J Neurol Neurosurg Psychiatry* 2017;**88**:12–18.
32. Chamberlain Alanna M, Brown Robert D, Alonso Alvaro, Gersh Bernard J, Killian Jill M, Weston Susan A, Roger Véronique L. No decline in the risk of stroke following incident atrial fibrillation since 2000 in the community: a concerning trend. *J Am Heart Assoc* 2016;**5**.
33. Wittkowsky AK. Effective anticoagulation therapy: defining the gap between clinical studies and clinical practice. *Am J Manag Care* 2004;**10**:S297–S306.
34. Coull AJ, Silver LE, Bull LM, Giles MF, Rothwell PM. Direct assessment of completeness of ascertainment in a stroke incidence study. *Stroke* 2004;**35**:2041–2045.
35. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, Gutnikov SA, Edwards P, Mant D, Sackley CM, Farmer A, Sandercock PAG, Dennis MS, Warlow CP, Bamford JM, Anslow P. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet* 2004;**363**:1925–1933.
36. Vinereanu Dragos, Lopes Renato D, Bahit María Cecilia, Xavier Denis, Jiang Jie, Al-Khalidi Hussein R, He Wensheng, Xian Ying, Ciobanu Andrea O, Kamath Deepak Y, Fox Kathleen A, Rao Meena P, Pokorney Sean D, Berwanger Otavio, Tajer Carlos, de Barros e Silva Pedro Gabriel Melo, Roettig Mayme L, Huo Yong, Granger Christopher B, Carbajales Justo, Ceferino Gómez Javier Neri, Principato Mario Bruno, Von Wulffen María Alejandra, Salvador Acunzo Jorge Galperín Rafael, Bonato Ricardo Renato, Ciampi Natalia, Marani Alberto Babil, Panigadi Cristian Gustavo, Pastura Silvia Gabriela, Onetto Leonardo Martín, Moya Cecilia Rafaela, Budassi Nadia, Valle Marisol, Camerini Daniel, Monjes Enrique, Zabala Federico, Ricart Juan Pablo, Medesani Luis, Ortuño Campos Eduardo Noe, Ferroni Fabián, Torres Mariana Foa, Fassi Daniel Omar, Díaz Bosio Fernando Javier, Pérez Baztarrica Gabriel Edgardo, Infantas Teresa Zúñiga, Perlo Daniela, García Celso Fernando, Durán Rubén García, Durán Luisina García, Pettinari Cecilia Alejandra, Vico Marisa Liliana, Lanchiotti Paulina Virginia, Gómez Mariela Soledad, Poy Carlos Alberto, Grazziani Franco Sebastián, Laspina Marcela Julieta, Poy María Laura, García Marilia, Egydio Flávia, Restelli Elissa, Kawakami Anelise, Soares Tamara Colaiácovo, Valois Mayara Vioto, Duarte Tauane Bello, Barbosa Lilian Mazza, de Paola Angelo Amato Vicenzo, Pimenta Thiago Librelon, Moro Jeronimo Gabriela Dal, da Costa Bruna S. Fernande, Coutinho Enia Lucia, Guerrero Andressa Zulmira A, Maia Lilia Nigro, Nakazone Marcelo Arruda, Teixeira Lemos Maria Angelica, Coelho Costa Osana Maria, Demore Ana Paula, Brito Roberta Parra, Bon Melo Camila Dal, Góes Nadielly Codonho, Lorenço Osvaldo, Maia Gonçalves Luiz Otavio, Nishiama Kátia, de Lima Tiago Aparecido Maschio, Backes Luciano Marcelo, de Lima Deucher Keyla Liliana Alves, Rodrigues Milena Pozzatto, Baldissera Dunnia Monisa, Caos Reolão José Basileu, dos Santos Tais Alves, Birck Freisleben Fernanda Michel, da Silveira Kaross Níncia Lucca, Montovani Jéssika Tzervieczenski, Cantarelli Maiara, Lucion Aline, Amarante Luciano do, Foscarini Priscila, de Mello Perez Claudia, França Fernanda Ribeiro, Fialho Lisa, Veiga Rey Helena Cramer, Good God Epotamenides Maria, Figueiredo Estêvão Lanna, Werner Gustavo Fonseca, de Faria Garcia Jose Carlos, Azevedo Bruna, Vianna Barbosa Luiz Carlos, Pardi Ernaldo, Oliveira Márcia Domingos, Martinelli Toshie, Cavalini Roseli Gomes, de Moraes Michele Santos Montoni, Lorga Filho Adalberto Menezes, Palmegiani Eduardo, Cury Megid Thiago Baccilli, Queirantes Clotildes SP, Arroyo Cruz Thamyres Santini, He Pengkang, Zhou Xiaolan, Zhou Na, Zhao Mingzhong, Yu Juan, Cheng Yong, Wang Lijun, Liu Lili, Liu Shuwang, Li Lei, Li Aihua, Yuan Xiaochen, Xia Guangwei, Wang Zhirong, Li Chengzong, Chen Wensu, Tang Qiang, Tang Qunzhong, Xu Weiting, Zhu Xinyi, Hou Bin, Ma Wenjian, Wang Chongquan, Jin Qiaoyun, Wang Jianan, Xie Xiaojie, Joseph Johny, Davidson Deepak, Thomas Joby K, Kunjumon Tony V, Stephen Tibin, Fatania Kamlesh, Rathi Gaurav, Garala Kinjal, Doshi Dhruval, Varghese Kiron, Srilakshmi MA, Sheeba Lumin, Kumar Shivendra, Rao Malipeddi Bhaskara, Rao Kodem Damodara, Vuriya Anjan Kumar, Kumari Mandula Padma, Khandelwal Bidita, Dhakal Mona, Srivastava Nitin, Khatri Dheeraj, Moktan Shova, Gupta Rajeev, Roy Sanjeeb, Kumawat Kapil, Sharma Mukesh, Sharma KK, Jathappa Narendra, Lokesh BH, Kariyappa Shilpa, Leela AC, Someshwara KC, Desai Soaham, Desai Devangi, Patel Kunj, Patel Sujal, Bhartiya Maulik, Mahanta Bhupendra Narayan, Dutta Dibya Jyoti, Rajkonwer Ghanashyam, Gupta Sandeep Kumar, Mishra Ashok Kumar, Singh Akansha, Kesarwani Naveen, Chioncel Ovidiu, Balan Adriana, Carstea Nicolae, Chitoiu Gabriel Tatu, Cornaciu Stelian, Cinteza Mircea, Rimbas Roxana C, Dimulescu Doina, Ionescu Luminita, Fruntelata Ana, Dumitru Nicoleta, Gaita Dan, Pleava Roxana, Iliesiu Adriana, Uscoiu Gabriela, Lighezan Daniel, Buzas Roxana, Sinescu Crina J, Avram Ana Maria, Baldea Sorina, Galrinho Ruxandra Dragoi, Magda Stefania L, Matei Lavinia. A multifaceted intervention to improve treatment with oral anticoagulants in atrial fibrillation (IMPACT-AF): an international, cluster-randomised trial. *Lancet* 2017;**390**:1737–1746.