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Clinical Research

Reassessing Cardiovascular Risk in Patients With Peripheral Artery Disease Undergoing Myocardial Perfusion Imaging

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ABSTRACT

Background: Coronary artery disease (CAD) and peripheral artery disease (PAD) are often regarded as analogous risk factors for major adverse cardiovascular events (MACE), given their shared pathophysiology. We aimed to investigate whether the elevated MACE risk in PAD is driven by myocardial perfusion abnormalities or through other PAD-specific mediators.

Methods: We analyzed 45,252 patients from an international, multicentre registry who underwent SPECT myocardial perfusion imaging, excluding those with early coronary revascularization (< 90 days). Myocardial perfusion abnormalities were quantified using total perfusion deficit (TPD). MACE was defined as all-cause mortality, unstable

RÉSUMÉ

Contexte : La coronaropathie et la maladie artérielle périphérique (MAP) sont souvent considérées comme des facteurs de risque analogues d'événements cardiovasculaires indésirables majeurs (ECIM), compte tenu de leur physiopathologie commune. Nous avons tâché de déterminer si le risque élevé d'ECIM en cas de MAP était dû à des anomalies de la perfusion myocardique ou à d'autres médiateurs spécifiques de la MAP.

Méthodologie : Nous avons analysé les données de 45 252 patients qui étaient inscrits dans un registre multicentrique international et qui avaient subi une imagerie de perfusion myocardique SPECT, en excluant les patients ayant subi une revascularisation coronarienne

With an estimated prevalence of more than 230 million worldwide, peripheral artery disease (PAD) poses a substantial health burden because of its high associated risk for cardiovascular mortality and morbidity.[1-3] Although PAD shares similar risk profiles to coronary atherosclerosis, the prognosis of individuals with concomitant PAD is worse than those with coronary artery disease (CAD) alone.[4,5] Previous studies have examined the influence of comorbidities, laboratory measurements, and clinical indices on outcomes of patients with PAD.[2,6,7] However, the prognostic significance of perfusion

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angina admission, myocardial infarction, or late coronary revascularization. PAD was defined using questionnaires or review of electronic medical records. Propensity-score matching was used to select balanced groups of patients with and without PAD.

Results: During a median follow-up of 3.6 years (interquartile range [IQR]: 2.6-4.8 years), 5932 patients (13.7%) experienced at least 1 MACE. Compared with patients with neither disease, isolated history of CAD (adjusted hazard ratio [aHR], 1.92; 95% confidence interval [CI], 1.80-2.05) conferred a similar MACE risk as concomitant history of CAD and PAD (aHR, 1.57; 95% CI, 1.44-1.71) and greater risk than isolated history of PAD (aHR, 1.20; 95% CI, 1.09-1.32; $P < 0.001$). After propensity-score matching, history of PAD alone was not independently associated with increased MACE risk ($P = 0.064$).

Conclusions: Although patients with PAD often have concomitant CAD and greater myocardial perfusion abnormalities, PAD itself was not linked to higher risk of MACE after adjusting for these factors. These findings highlight the importance of assessing myocardial ischemic burden in PAD for risk stratification and prompt initiation of disease-modifying therapies.

précoce (< 90 jours). Les anomalies de la perfusion myocardique ont été quantifiées à l'aide du déficit total de perfusion (DTP). Les ECIM étaient définis comme la mortalité toutes causes confondues, l'admission pour angine instable, l'infarctus du myocarde ou la revascularisation coronarienne tardive. La MAP a été définie à l'aide de questionnaires ou d'un examen des dossiers médicaux électroniques. Nous avons utilisé la correspondance des scores de propension pour obtenir des groupes équilibrés de patients avec et sans MAP.

Résultats : Durant un suivi médian de 3,6 ans (intervalle interquartile [IIQ] : 2,6 à 4,8 ans), 5 932 patients (13,7 %) ont présenté au moins un ECIM. Comparativement aux patients qui n'étaient pas malades, la présence d'antécédents isolés de coronaropathie (rapport des risques instantanés [RRI] ajusté : 1,92; intervalle de confiance [IC] à 95 % : 1,80 à 2,05) conférait un risque d'ECIM semblable à celui observé en cas d'antécédents concomitants de coronaropathie et de MAP (RRI ajusté : 1,57; IC à 95 % : 1,44 à 1,71) et un risque plus élevé qu'en cas d'antécédents isolés de MAP (RRI ajusté : 1,20; IC à 95 % : 1,09 à 1,32; $p < 0,001$). Après appariement en fonction des scores de propension, aucun lien indépendant n'a été établi entre les antécédents de MAP seuls et un risque accru d'ECIM ($p = 0,064$).

Conclusions : Bien que les patients atteints de MAP présentent souvent une coronaropathie concomitante et des anomalies de la perfusion myocardique plus importantes, la MAP en elle-même n'a pas été associée à un risque plus élevé d'ECIM après ajustement pour tenir compte de ces facteurs. Ces résultats soulignent l'importance d'évaluer le fardeau de l'ischémie myocardique en cas de MAP pour la stratification du risque et l'instauration rapide d'un traitement modificateur de la maladie.

deficit from myocardial perfusion imaging (MPI) with single-photon emission computed tomography (SPECT) has not yet been explored in this population.

Total perfusion deficit (TPD) derived from automated quantification of SPECT MPI has been increasingly employed in studies to assess the extent of myocardial perfusion abnormalities and associated risk for major adverse cardiovascular events (MACE). The incremental prognostic value of TPD for MACE has been demonstrated in CAD, obesity, diabetes, and the general population of patients undergoing SPECT MPI.[8-11] Furthermore, stress TPD has been identified as the best individual predictor of MACE among a machine-learning panel that consisted of 70 parameters, including imaging, stress testing, and clinical variables.[12] Given that PAD is associated with more extensive coronary atherosclerosis, this study aims to evaluate the prognostic importance of myocardial perfusion among patients with PAD and to determine whether PAD independently contributes to risk of MACE beyond concomitant CAD and myocardial perfusion abnormalities.

Methods

Study population

The **Re**gistry of **F**ast Myocardial Perfusion **I**maging with **Ne**xt Generation SPECT (REFINE SPECT) is an international, multicentre, observational cohort study of patients undergoing SPECT MPI with cadmium zinc telluride cameras designed to evaluate diagnosis and prognosis using quantitative SPECT MPI parameters. Medical history was collected at the time of clinical reporting and transferred with other clinical data to the central core laboratory at Cedars-Sinai Medical Center after deidentification. History of PAD was defined using either medical history questionnaires (including history of PAD or claudication symptoms) performed at the time of imaging or with review of electronic medical records using previously validated ICD-10 codes, which include upper and lower extremity vascular disorders as well as mesenteric vascular disease.[13] History of CAD was defined as history of myocardial infarction or previous coronary revascularization (with percutaneous coronary intervention or coronary artery bypass grafting).[14] Since its conception, 45,252 patients have been enrolled into the REFINE SPECT registry from 13 centres.[15] We excluded patients who underwent coronary revascularization within 90 days (n = 1963) of imaging in the primary analysis, as this may alter the relationship between MPI findings and clinical outcomes.[16,17] The overall study design is outlined in the Central Illustration. The institutional review board committees approved the study protocol at each participating centre and the core laboratory. Patients either provided written informed consent or a waiver of consent was provided for use of retrospective data based on site-specific protocols.

Imaging protocols

SPECT MPI scanning was performed according to the American Society of Nuclear Cardiology MPI guidelines.[18] Patients underwent either symptom-limited exercise stress or pharmacologic stress testing combined with low-level exercise when possible. Medical history was ascertained at each site as previously described.[15] This study specifically evaluated

patients with history of PAD and compared them with those with both history of PAD and previous history of CAD, as well as to those with either or neither condition.

Image quantification

Deidentified images were transferred from each participating centre to the core laboratory. Experienced core laboratory technologists conducted quality control and were blinded regarding clinical and prognostic information. TPD was quantified using Quantitative Perfusion SPECT (Cedars-Sinai Medical Center, Los Angeles, California, USA) and used in all analyses. Left ventricular ejection fraction (LVEF) and left ventricular end-diastolic volume (LVEDV) were quantified from gated stress images using Quantitative Gated SPECT software programs (Cedars-Sinai Medical Center, Los Angeles, CA). Stress myocardial perfusion deficits were categorized as: no deficit (TPD = 0%), very minimal deficit (0% < TPD < 1%), minimal deficit (1% ≦ TPD < 5%), mild deficit (5% ≦ TPD <10%), and moderate-to-severe deficit (TPD ≥ 10%).[8]

Outcome assessment

The primary endpoint was MACE, defined as a composite of all-cause mortality, myocardial infarction, unstable angina requiring hospitalization, and late coronary revascularization (> 90 days after image acquisition). Patient follow-up was performed locally at each participating center according to site-specific protocols as previously described.[15]

Statistical analysis

Continuous variables are presented as medians with interquartile range (IQR) or mean ± standard deviation if normally distributed. Categorical variables are summarized as frequencies (proportion) and compared using χ^2 or Fisher exact test as appropriate.

To identify a cohort of patients with similar characteristics as those with PAD, we used a 1:1 nearest neighbour matching using a calliper of 0.01. The propensity score included age, sex, body mass index (BMI), previous history of CAD, hypertension, diabetes, dyslipidemia, smoking status, family history of CAD, type of stress test (pharmacology or exercise), stress TPD, LVEF, and LVEDV. Standardized differences were used to assess the balance between matched cohorts.[19] In addition, we performed a sensitivity analysis that included the subset of patients who underwent early coronary revascularization (n = 1963) and applied the same propensity score-adjusted analysis but incorporated early revascularization as a covariate in the regression model.

Associations with MACE were assessed using Cox proportional hazards regression and Kaplan-Meier survival analyses. The adjusted hazard ratio (aHR) was reported with 95% confidence intervals (CIs). Multivariable models were adjusted for age, sex, BMI, hypertension, diabetes, dyslipidemia, smoking status, family history of CAD, type of stress test, LVEDV, and LVEF. A mediation analysis accounting for these clinical covariates was performed for the interaction between previous history of CAD and PAD on MACE using the PROCESS version 4.3 macro with 5000 bias-corrected bootstrap samples.[20] Statistical significance was considered based on 2-tailed $P < 0.05$. All statistical analyses were performed using SPSS, version 26 (IBM Corporation, Armonk, NY) and R 4.3.2 (R Studio for Statistical Analysis, Vienna, Austria).

Results

Baseline patient characteristics

A total of 43,289 patients were included from the REFINE SPECT registry; of those, 29,566 had neither history of CAD nor PAD, 3714 had isolated history of PAD, 5675 had isolated history of CAD, and 4334 had a history of both CAD and PAD (Supplemental Table S1). Patients with concomitant history of PAD and history of CAD were more likely to be male (76.3% vs 61.3%, $P < 0.001$) and have hypertension (85.4% vs 78.9%, $P < 0.001$), or dyslipidemia (69.4% vs 42.1%, $P < 0.001$) than patients with isolated history of PAD. In addition, patients with concomitant history of PAD and history of CAD had greater stress TPD (median 5.6% vs 3.3%, $P < 0.001$), LVEDV (median 91.2 vs 81.2 mL, $P < 0.001$), and lower LVEF (median 59.5 vs 64.4%, $P < 0.001$) than patients with isolated PAD (Fig. 1). Notably, patients with history of CAD alone had only slightly lower ischemic TPD values compared with patients with both history of CAD and PAD (median 3.1 vs 3.4%, $P = 0.014$).

Table 1 shows the overall population characteristics before and after propensity-score matching. Before matching, patients with history of PAD were older (69 vs 64 years, $P < 0.001$), more often male patients (69.4% vs 51.7%, $P < 0.001$), smokers (42.9% vs 19.4%, $P < 0.001$), and had a higher prevalence of previous history of CAD (53.9% vs 16.1%, $P < 0.001$). The presence of PAD was associated with more extensive stress TPD (4.4% vs 2.5%, $P < 0.001$). Similarly, there were more patients with PAD having mild (21.1% vs 17.2%, $P < 0.001$) and moderate-to-severe perfusion deficit (24.8% vs 11.4%, $P < 0.001$) than patients without history of PAD. However, the proportions of patients in each TPD category became comparable following propensity-score matching.

Risk of MACE based on PAD and previous CAD status

During a median follow-up of 3.6 years (IQR: 2.6-4.8 years), 5932 patients (13.7%) experienced at least 1 MACE, including 3362 all-cause mortality, 892 nonfatal myocardial infarction, 809 admissions for unstable angina, and 2160 late coronary revascularizations (> 90 days). Patients with histories of CAD alone or a history of both CAD and PAD were at the highest risk of MACE (Fig. 2). However, history of PAD alone did not confer a similar MACE risk as history of CAD. This is further evidenced in the multivariable Cox regression model, in which—compared with patients without previous histories of CAD or PAD—a history of both CAD and PAD (aHR, 1.57; 95% CI, 1.44-1.71) and isolated history of CAD (aHR, 1.92; 95% CI, 1.80-2.05) conferred a significantly greater risk for MACE than isolated history of PAD (aHR, 1.20; 95% CI, 1.09-1.32), after adjusting for other traditional cardiovascular risk factors (Supplemental Table S2).

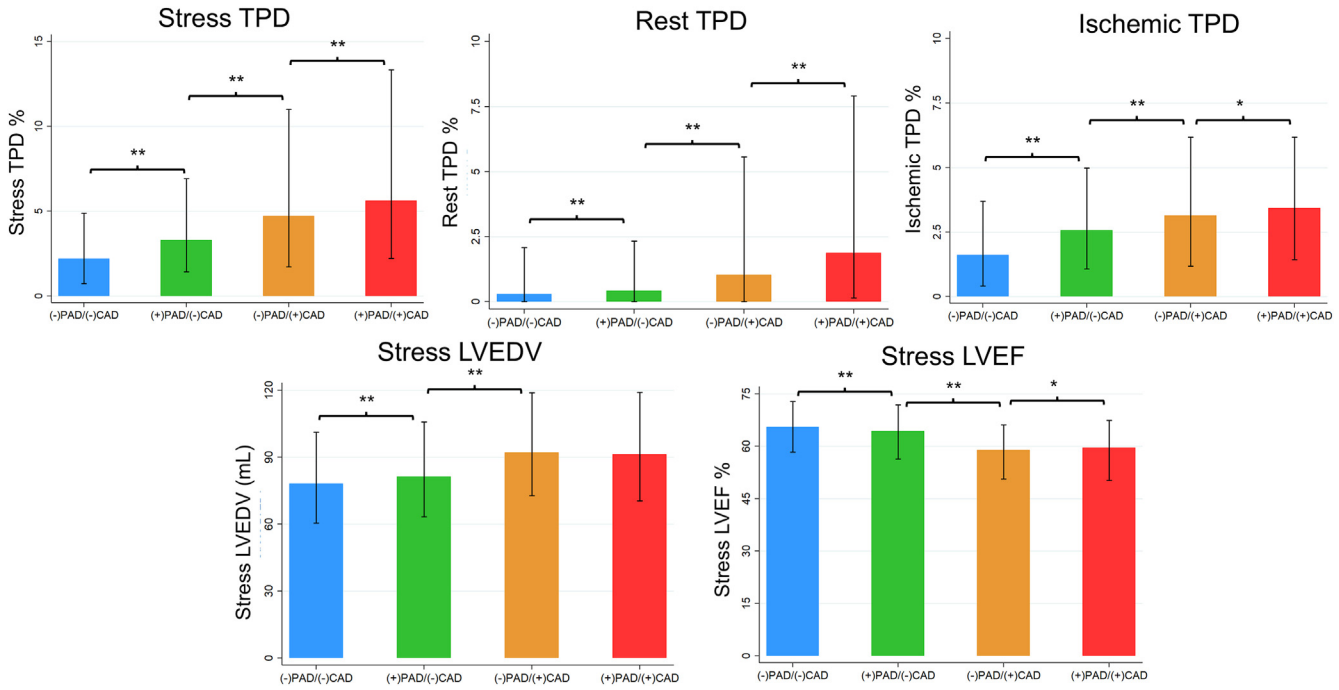


Figure 1. Single photon emission computed tomography (SPECT) imaging parameters based on peripheral artery disease (PAD) and previous coronary artery disease (CAD) status. Parameters include stress total perfusion deficit, rest total perfusion deficit, ischemic total perfusion deficit, left ventricular end diastolic volume, and left ventricular ejection fraction. $*P < 0.01$, $**P < 0.001$ between groups. TPD, total perfusion deficit.

When we examined the relative distribution of MACE categories among clinical phenotypes, we found that in patients without history of PAD or previous CAD, MACE was predominantly driven by all-cause mortality, whereas patients with histories of PAD or histories of CAD were more likely to experience MACE related to late coronary revascularization (Supplemental Fig. S1). Nevertheless, the incidence of MACE remained highest in patients with previous histories of CAD or histories of both CAD and PAD across all MACE categories compared with patients without either disease or with isolated history of PAD.

Table 1. Clinical characteristics of study participants before and after propensity score matching

	Before match			After match		
	Patients with PAD (n = 8048)	Patients without PAD (n = 35,241)	Std Diff	Patients with PAD (n = 7022)	Patients without PAD (n = 7022)	Std Diff
Age (years)	69 (62-76)	64 (56-72)	0.412	69 (61-76)	69 (61-76)	0.019
Sex (Male)	5582 (69.4)	18230 (51.7)	0.367	4684 (66.7)	4715 (67.1)	0.009
BMI (kg/m^2)	28.1 (25.0, 31.9)	28.9 (25.3, 32.4)	0.121	28.5 (25.1, 31.3)	28.3 (25.1, 32.0)	0.006
Medical history						
Hypertension	6630 (82.4)	20873 (59.2)	0.527	5608 (79.9)	5619 (80.0)	0.004
Diabetes	2777 (34.5)	8764 (24.9)	0.212	2379 (33.9)	2340 (33.3)	0.012
Dyslipidemia	4570 (56.8)	17337 (49.2)	0.152	4069 (57.9)	3946 (56.2)	0.035
Family history of CAD	3018 (37.5)	10534 (29.9)	0.161	2420 (34.5)	2463 (35.1)	0.013
Smoking	3452 (42.9)	6846 (19.4)	0.524	2496 (35.5)	2483 (35.4)	0.004
Prior history of CAD	4334 (53.9)	5675 (16.1)	0.862	3321 (47.3)	3311 (47.2)	0.003
Exercise stress	3583 (44.5)	17770 (50.4)	0.118	3096 (44.1)	3066 (43.7)	0.009
Imaging variables						
LVEDV	86.3 (66.0, 112.0)	78.8 (60.7, 101.8)	0.221	84.8 (65.0, 109.9)	84.8 (65.4, 109.6)	0.009
LVEF	61.7 (52.8, 69.5)	64.0 (56.6, 71.4)	0.241	62.2 (53.5, 70.0)	61.9 (53.4, 69.3)	0.016
Stress TPD	4.4 (1.8, 9.9)	2.5 (0.9, 5.6)	0.410	4.0 (1.7, 8.8)	3.9 (1.5, 8.8)	0.008
TPD category						
TPD = 0	307 (3.8)	2788 (7.9)	0.088	284 (4.0)	341 (4.9)	0.020
0% < TPD <1%	863 (10.7)	6884 (19.5)	0.248	807 (11.5)	1001 (14.3)	0.083
1% ≤ TPD <5%	3184 (39.6)	15505 (44.0)	0.090	2911 (41.5)	2688 (38.3)	0.065
5% ≤ TPD ≤10%	1699 (21.1)	6061 (17.2)	0.100	1477 (21.0)	1437 (20.5)	0.014
TPD > 10%	1995 (24.8)	4003 (11.4)	0.354	1543 (22.0)	1555 (22.1)	0.004

Data are presented as median with interquartile range or n (%).

BMI, body mass index; CAD, coronary artery disease; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; PAD, peripheral artery disease; SD, standard deviation; TPD, total perfusion deficit.

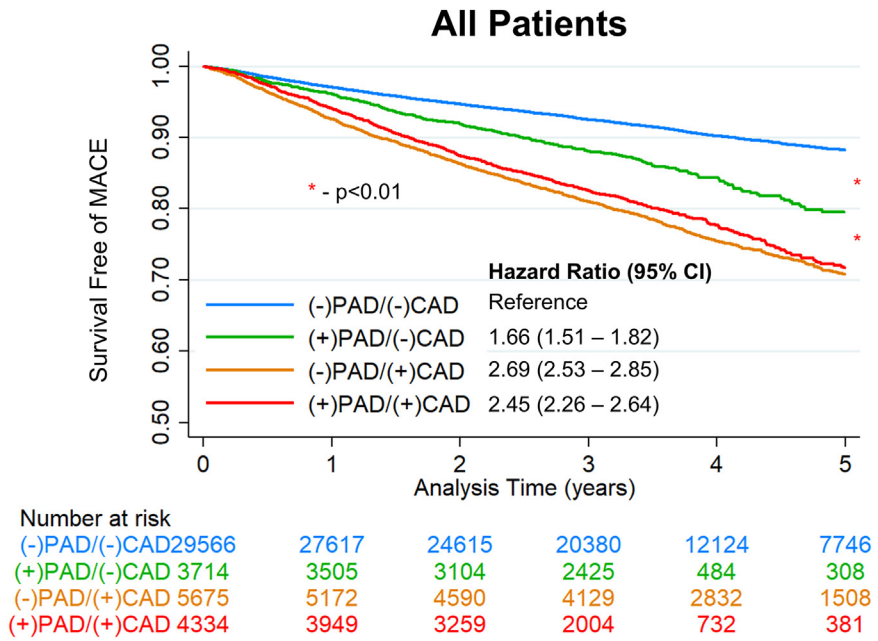


Figure 2. Kaplan-Meier curves for major adverse cardiovascular events (MACE) according to the presence of peripheral artery disease (PAD) and previous coronary artery disease (CAD). CI, confidence interval.

Risk of MACE across TPD categories

Before propensity-score matching, patients with history of PAD experienced significantly more MACE than patients without a history of PAD (16.4% vs 13.1%, $P < 0.001$, Fig. 3A). When patients were stratified based on TPD categories, there was a substantial reduction in MACE-free survival with the presence of history of PAD across the spectrum of myocardial perfusion abnormalities ($P < 0.001$), except for patients within the moderate to severe perfusion deficit range (TPD > 10%, Fig. 4). However, after adjusting for relevant imaging parameters and comorbidities, including previous history of CAD and stress TPD, patients with history of PAD exhibited a similar risk for MACE as patients without histories of PAD ($P = 0.064$, Fig. 3B). Moreover, we only observed a higher risk of MACE associated with the history of PAD in the very minimal perfusion deficit category (0% < TPD < 1%, $P = 0.006$, Fig. 4). Based on the mediation analysis, history of previous CAD moderated the relationship between history of PAD and MACE, in which history of PAD alone (β −0.05; 95% CI −0.18 to 0.09) did not directly increase MACE risk after accounting for clinical covariates (Supplemental Table S3). In comparison, the interaction between previous CAD and PAD (β −0.53; 95% CI −0.71 to −0.35) was independently associated with elevated risk of MACE, highlighting the critical role of CAD in driving adverse outcomes in patients with histories of PAD.

Rise in severity of TPD was independently associated with an incremental increase in risk of MACE for patients without PAD following multivariable adjustment (Table 2). Among patients with histories of PAD, the presence of myocardial perfusion deficit was also associated with elevated risk of MACE but to a similar extent between those with very minimal (aHR, 1.88; 95% CI, 1.20-2.93), mild (aHR, 1.87; 95% CI, 1.21-2.88), and moderate-to-severe perfusion deficit (aHR, 1.98; 95% CI, 1.28-3.08). In the sensitivity analysis, there was a significant interaction between severity of TPD, early revascularization, and association with MACE (interaction $P < 0.001$), in which the risk of MACE was attenuated by early revascularization with greater severity of TPD in patients with histories of PAD (aHR, 0.80; 95% CI, 0.71-0.90) and without PAD (aHR, 0.67; 95% CI, 0.59-0.76, Supplemental Table S4).

Discussion

Using data from the large multicentre international REFINE SPECT registry, we evaluated the prognostic significance and predictors of MACE among patients with histories of PAD. Our results suggest that patients with histories of PAD had more extensive myocardial perfusion deficits on SPECT imaging and a higher prevalence of concomitant CAD, which conferred an elevated risk of MACE across most perfusion abnormality categories, except for those with the most severe perfusion deficits (TPD > 10%). However, after risk adjustment of these factors with propensity-score matching, history of PAD alone was not independently associated with increased risk of MACE, except in patients with very minimal perfusion deficit (0% < TPD < 1%). These findings indicate that history of CAD and myocardial perfusion abnormalities serve as the predominant drivers of adverse cardiac outcomes in patients with histories of PAD undergoing SPECT MPI. Importantly, our study highlights the importance of identifying myocardial perfusion abnormalities in patients with histories of PAD to mitigate future risk of MACE through timely intervention.

Patients with PAD have a considerably greater burden of myocardial ischemia, with coronary complications being the leading cause of mortality in this population, accounting for 40% to 60% of cases. SPECT MPI remains the dominant modality for routine noninvasive assessment of clinical and subclinical myocardial ischemia while demonstrating enhanced utility for prognostication of cardiovascular outcomes.[8,12,21,22] Previous research has established the prognostic importance of subtle perfusion defects (findings below standard visual or quantitative

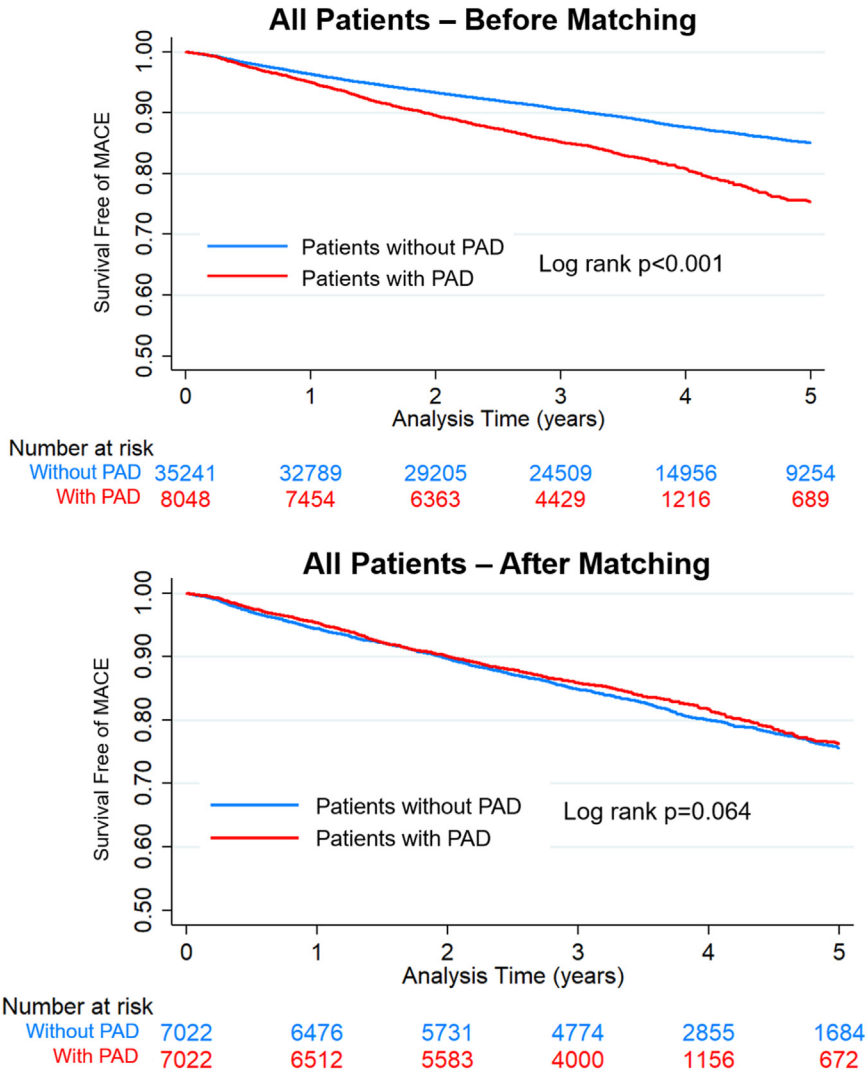


Figure 3. Kaplan-Meier curves for major adverse cardiovascular events (MACE) before and after propensity score matching between patients with peripheral artery disease (PAD) and without PAD.

abnormality thresholds) in patients with obesity, diabetes, and individuals without known CAD.[8,10,11] Our findings expand this understanding by demonstrating that PAD conferred a greater risk for MACE in patients with subtle changes in myocardial perfusion (reflected by the 0% to < 1% TPD category), even after accounting for relevant comorbidities and imaging findings. Interestingly, this association was not observed in patients with the most severe perfusion deficits (TPD > 10%), in which history of PAD did not significantly influence risk of MACE. This pattern contrasts with the effect of diabetes, which demonstrated its strongest risk for MACE in patients with severe perfusion deficits compared with other TPD categories.[10]

Our study found that patients with concomitant histories of PAD and previous history of CAD displayed more significant myocardial perfusion deficits than patients with isolated histories of PAD, translating to a greater risk of MACE. These results corroborate with existing evidence, including the **E**xamining **U**se of Ti**c**agre**l**or **i**n Peripheral Artery **D**isease (EUCLID) trial, which showed a nearly fivefold relative increase in risk of composite cardiovascular death, myocardial infarction, or ischemic stroke in patients with combined PAD and CAD vs PAD alone.[23] Similarly, the **F**urther Cardiovascular **Ou**tcomes **R**esearch With PCSK9 **I**nhibition in Subjects With **E**levated **R**isk (FOURIER) trial revealed that 14.9% of placebo-treated patients with PAD and previous myocardial infarction experienced MACE compared with 10.3% of those with PAD alone.[24] Moreover, the **X**arelto Plus **A**cetylsalicylic Acid: **T**reatment Patterns and **O**utcomes in Patients With **A**therosclerosis (XATOA) registry reported that MACE or major adverse limb events were 9.16 vs 2.48 per 100 patient-years in patients with vs without polyvascular disease, respectively.[25] Taken together, these findings consistently demonstrate that polyvascular involvement in patients with PAD portends substantially increased MACE risk and mortality, underscoring the importance of comprehensive cardiovascular risk assessment in this population.[23,26]

We demonstrate that myocardial perfusion is a key driver of MACE risk in patients with histories of PAD undergoing MPI. Mediation analysis identified previous

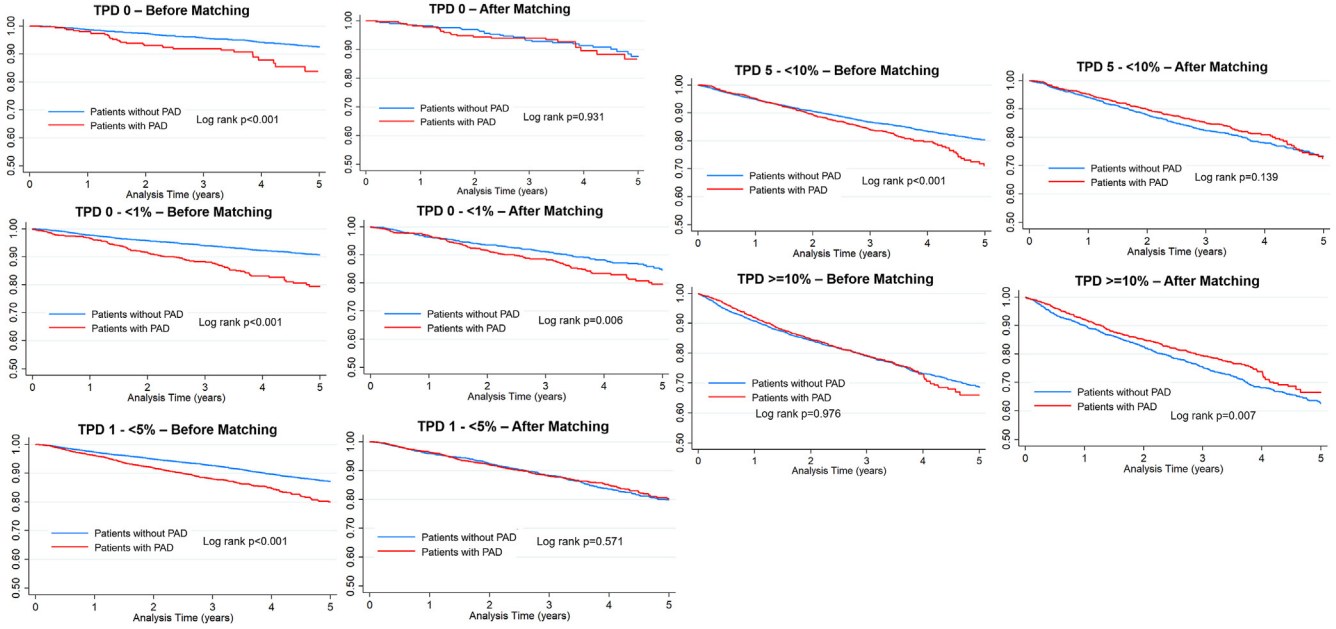
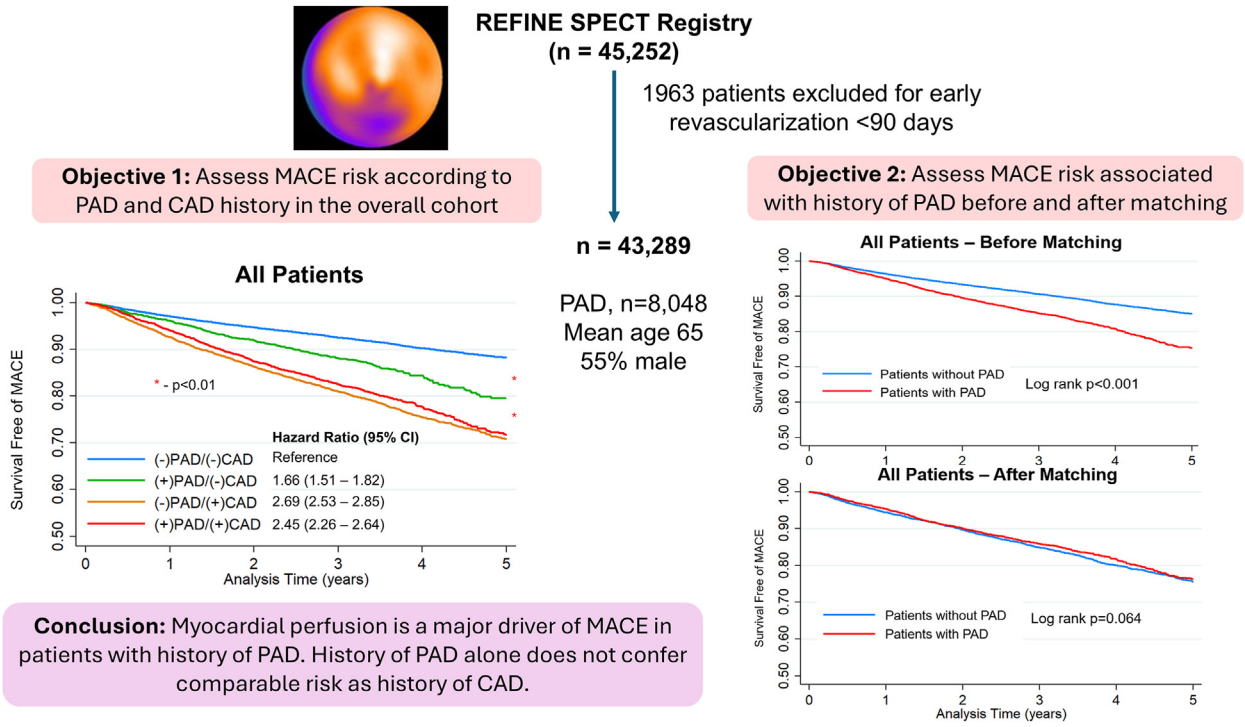


Figure 4. Kaplan-Meier curves for major adverse cardiovascular events (MACE) between patients with peripheral artery disease (PAD) and without PAD according to TPD category before and after propensity score matching. Patients undergoing SPECT MPI were stratified based on normal perfusion (TPD = 0%), very minimal perfusion deficit (0% < TPD < 1%), minimal perfusion deficit (1% ≤ TPD < 5%), mild perfusion deficit (5% ≤ TPD ≤ 10%), and moderate to severe perfusion deficit (TPD > 10%). SPECT, single photon emission computed tomography; TPD, total perfusion deficit.



Central Illustration. Overview of the study design. We evaluated risk of major adverse cardiovascular events (MACE) in patients with peripheral artery disease (PAD) from the **Re**gistry of **F**ast Myocardial Perfusion **I**maging with **Ne**xt Generation SPECT (REFINE SPECT).

Table 2. Cox regression analysis for MACE of stress TPD categories

	Patients with PAD		Patients without PAD		
	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value	Interaction *P* value
Age, per 5 years	1.07 (1.03-1.10)	< 0.001	1.14 (1.11-1.18)	< 0.001	0.011
Male	1.00 (0.87-1.16)	0.954	0.84 (0.74-0.96)	0.007	0.502
BMI, per 5 kg/m^2	0.88 (0.83-0.93)	< 0.001	0.94 (0.89-0.99)	0.018	0.662
Hypertension	1.30 (1.10-1.52)	0.002	0.99 (0.87-1.13)	0.907	0.008
Diabetes	1.47 (1.30-1.66)	< 0.001	1.25 (1.12-1.39)	< 0.001	0.029
Dyslipidemia	0.89 (0.78-1.01)	0.072	0.86 (0.77-0.96)	0.010	0.556
Smoking	1.06 (0.93-1.21)	0.373	1.18 (1.05-1.32)	0.006	0.953
Family history of CAD	0.92 (0.81-1.05)	0.222	0.86 (0.76-0.97)	0.015	0.356
Prior CAD	1.25 (1.10-1.43)	0.001	1.68 (1.48-1.90)	< 0.001	0.003
Exercise stress	0.56 (0.48-0.64)	< 0.001	0.75 (0.67-0.84)	< 0.001	0.019
LVEDV, per 10 mm^3	1.02 (1.00-1.03)	0.043	1.02 (1.01-1.04)	0.002	< 0.001
LVEF, per 5%	0.94 (0.91-0.97)	< 0.001	0.94 (0.91-0.96)	< 0.001	0.307
TPD category					
TPD = 0	(Reference)	-	(Reference)	-	-
0% < TPD < 1%	1.88 (1.20-2.93)	0.006	1.43 (0.97-2.11)	0.072	0.329
1% ≤ TPD < 5%	1.58 (1.04-2.41)	0.034	1.69 (1.18-2.43)	0.005	0.828
5% ≤ TPD ≤ 10%	1.87 (1.21-2.88)	0.005	2.06 (1.43-2.98)	< 0.001	0.719
TPD > 10%	1.98 (1.28-3.08)	0.002	2.17 (1.49-3.14)	< 0.001	0.607

The extent of perfusion defect is defined as no deficit (TPD = 0%), very minimal deficit (0% < TPD < 1%), minimal deficit (1% ≤ TPD < 5%), mild deficit (5% ≤ TPD ≤ 10%), and moderate-to-severe deficit (TPD > 10%).

aHR, adjusted hazard ratio; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; PAD, peripheral artery disease; TPD, total perfusion deficit during stress.

history of CAD as the principal mediator of elevated cardiovascular risk associated with PAD. Although current Canadian and European PAD management guidelines do not recommend routine screening for asymptomatic CAD because of insufficient evidence of clinical benefit, they recognize the substantial cardiovascular risk posed by the high prevalence of polyvascular disease in this population.[27,28] Given our results, we propose more aggressive pursuit of CAD screening, particularly in symptomatic patients with PAD, to optimize medical therapy and improve risk stratification. Even patients with stable PAD may benefit from screening for subclinical CAD and evaluation of myocardial ischemia. Further research is needed to identify which subgroups of patients with PAD would derive the most benefit from screening.

Although PAD is characterized by atherosclerotic or thrombotic occlusions of lower extremities, the presence of PAD has also been linked to greater expansion of coronary atheroma volume, calcification, and constrictive arterial remodelling in CAD.[29] We observed that the combination of previous CAD and PAD correlated with more extensive stress myocardial perfusion defects during MPI than isolated CAD, which is partially attributable to greater resting TPD. Indeed, PAD may exacerbate resting myocardial perfusion abnormalities through microvascular dysfunction and systematic inflammation.[30] It has been hypothesized that atherosclerotic plaques in large vascular beds of peripheral limbs may release inflammatory mediators that directly contributes to development of CAD.[31] Supporting this, serum from the affected limb of patients with PAD (unlike CAD-only patients), induced proinflammatory changes in human coronary artery endothelial cells, correlating with elevated neutrophil myeloperoxidase and interleukin (IL)-6 levels in the femoral circulation and progressive coronary artery endothelial dysfunction.[32] Conversely, coronary vascular impairment perpetuates the extent of myocardial ischemia and reduces myocardial blood flow reserve, further increasing mortality risk in patients with PAD.[33]

Based on the mechanisms of atherosclerosis in PAD, contemporary guidelines emphasize a combined approach targeting lipid metabolism, thrombosis, and inflammation to reduce future MACE.[30,34] Current Canadian and American guidelines recommend an low-density lipoprotein- cholesterol (LDL-C) target of < 1.8 mmol/L, whereas European guidelines propose a more intensive goal of < 1.4 mmol/L, particularly for those with symptomatic PAD or polyvascular disease.[35-37] This aggressive lipid-lowering approach has demonstrated substantial reductions in progression of coronary atherosclerosis among patients with PAD.[29] For antithrombotic therapy, the **C**ardiovascular **O**utco**m**es for **P**eople Using **A**nticoagulation **S**trategie**s** (COMPASS) trial established the efficacy of low-dose rivaroxaban combined with aspirin in high-risk patients with PAD,[34] whereas alternative antiplatelet agents such as clopidogrel and ticagrelor have shown additional MACE reduction benefits over aspirin in PAD.[27] However, even with optimal lipid control and antithrombotic therapy, residual inflammatory risk persists, as evidenced by elevated markers such as C-reactive protein (CRP) and IL-6, which prompted investigation into targeted anti-inflammatory therapies such as colchicine for atherosclerotic disease.[30] Despite their evidence in reducing inflammation-driven cardiovascular risk, further studies are needed to confirm their efficacy, specifically in the PAD population. Our findings underscore the clinical importance of early detection of myocardial perfusion abnormalities in patients with PAD, especially given that these evidence-based therapies remain underused for management of PAD.[34]

Limitations

The current analysis is limited by its observational nature. As such, clinical decision making of individual

physicians and different standards of practice at participating institutions may influence study endpoints such as decision and timing of coronary revascularization. The decision making for late coronary revascularization during long-term follow-up may not be guided by PAD status in practice but rather by the progression of symptoms, reduction in quality-of-life, and anatomic findings of coronary artery stenosis amendable to reperfusion. Accordingly, only 15% of patients with moderate-to-severe stress TPD defects received early coronary revascularization. In addition, it is conceivable that findings of abnormalities in myocardial perfusion may prompt the initiation and uptitration of medical therapies. However, we were not able to monitor the effect of baseline medications and therapy initiation in patients following their SPECT MPI, which can influence the incidence of MACE in our patient population.

Moreover, we relied on medical history to identify patients with significant PAD. As a result, some patients with neurogenic claudication may have been erroneously labelled as having PAD, and many patients with subclinical PAD would be classified as not having PAD. Similarly, patients may have severe underlying CAD without a documented history of CAD before the time of imaging. However, this classification is reflective of the clinical information that would be routinely available among patients referred for SPECT MPI. We were also limited in the anatomic assessment of coronary vasculature, such as the coronary artery calcium score, which may provide a better distinction between patients with concomitant PAD and CAD from those with isolated CAD beyond perfusion deficits on MPI. Finally, as most clinical trials examining the use of medical therapies in PAD only demonstrated cardiovascular and mortality benefits in patients with symptomatic PAD, future subgroup analyses should focus on the disparity between symptomatic and asymptomatic PAD regarding myocardial ischemic burden and risks of MACE to guide clinical decision making.

Conclusions

Our study challenges the traditional view of CAD and PAD as analogous risk factors for adverse cardiovascular outcomes despite sharing similar pathophysiological mechanisms, including atherosclerotic lesions, endothelial dysfunction, and systemic inflammation. Based on results from the large international cohort of patients undergoing MPI, we demonstrated that the increased incidence of MACE associated with PAD is primarily driven by concurrent myocardial ischemia. The presence of PAD was associated with more extensive myocardial perfusion deficit and a higher prevalence of CAD, which conferred an elevated risk of MACE in patients across TPD categories except for the most severe perfusion deficits. After adjustment of clinical and imaging risk factors, PAD yields greater risk of MACE only in patients with very minimum perfusion deficit ($0\% < \text{TPD} < 1\%$). Therefore, a careful assessment of myocardial ischemic burden in patients with PAD is essential for prognostication and prompt introduction of disease modifying therapies aimed at reducing future MACE.

Ethics Statement

This research complied with the declaration of Helsinki. The institutional review board committees approved the study protocol at each participating centre and the core laboratory.

Patient Consent

Patients either provided written informed consent or a waiver of consent was provided for use of retrospective data based on site-specific protocols.

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Supplementary Material

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