Major Adverse Cardiovascular Events and Mortality

in Peripheral Artery Disease

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TABLE OF CONTENTS

ABSTRACT OF THESIS

Peripheral artery disease (PAD) is the third most prevalent atherosclerotic disorder after coronary artery and cerebrovascular disease. Irrespective of how it manifests clinically, PAD is consistently linked with excessive rates of major adverse cardiovascular events (MACE) and mortality. This thesis examines many contributing factors and provides new insights into the management of patients with this condition.

The introductory chapter considers the evidence for treating individual risk factors and the prescription of guideline-recommended medications in PAD. Many prior observational studies have found an under-prescription of therapies and suboptimal risk factor control in PAD, compared with coronary artery disease-only. It is known from diabetes studies that control of multiple risk factors can have a complex interaction, whereby the sum of the parts does not equal the whole. Multiple risk factor control is recommended universally, although little is known regarding the effect on PAD.

Chapter 2 is a post hoc analysis of the ACCELERATE trial that included 12,092 patients with atherosclerotic cardiovascular disease. The rates of MACE are compared between PAD and coronary artery disease-only patients in the setting of individual and combined risk factor control.

It is believed that PAD patients have high-risk coronary artery plaque that is more critical, diffuse and prone to thrombotic occlusion, but this has not been proven. Chapter 3 pools data from three clinical trials of lipid-lowering therapy, whereby, coronary artery disease was monitored using serial intravascular ultrasound imaging. Plaque burden and disease progression are compared between PAD and non-PAD patients, according to risk factor control.

Individual PAD studies indicate that there are gender discrepancies in symptoms, functional status, and treatment utilisation. It remains uncertain whether this translates to different long-term outcomes. Chapter 4 is a systematic review and meta-analysis to assess gender differences in MACE and mortality. Chapter 5 evaluates the gender differences in outcomes for the PAD patients from ACCELERATE.

Lower extremity revascularisation, either through endovascular or surgical means, can be complicated by major adverse limb events and mortality. Persisting debate exists as to which approach has greater long-term durability and outcomes. Chapter 6 compares the long-term outcomes of endovascular and surgical revascularisation in unmatched and propensity-score matched groups.

Dysfunctional high-density lipoprotein cholesterol (HDL-C) is an emerging cardiovascular risk factor that could be a therapeutic target. Previously, qualitative abnormalities of HDL-C were observed in Indigenous Australians, when they were compared to non-Indigenous Australians. Chapter 7 tests for an association between dysfunctional HDL and early PAD in Indigenous Australians.

Significant health disparities are affecting young Indigenous Australians. The estimation of cardiovascular risk is especially problematic in this population. Chapter 8 reviews a young Indigenous group that was screened for PAD. Their risk of cardiovascular disease is estimated using traditional Framingham-based algorithms.

Questions remain whether all patients with PAD should be treated with the most intensive therapies, or if there is a role for a risk-stratified approach akin to atrial fibrillation management. Chapter 9 evaluates several CHADS2-based scores for predicting MACE in PAD following hospital presentations, compared with clinical manifestations of other vascular territories.

DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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“It’s not where you go, it’s who you meet along the way.”

- **The Wizard of Oz**

SCHOLARSHIPS, ABSTRACTS AND PUBLICATIONS

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- Faculty of Health Sciences Divisional Scholarship (2017 – 2020)

Abstract

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LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ABI	Ankle-brachial index
AF	Atrial fibrillation
AHA	American Heart Association
ALI	Acute limb ischaemia
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
CLI	Critical limb ischaemia
CI	Confidence interval
CV	Cardiovascular
CVA	Cerebrovascular accident
DBP	Diastolic blood pressure
EEM	External elastic membrane
ESC	European Society of Cardiology
HbA1c	Glycosylated haemoglobin
HDL-C	High-density lipoprotein cholesterol
HDL CEC	High-density lipoprotein-mediated cholesterol efflux capacity
HotH	Heart of the Heart
HR	Hazard ratio
Hs-CRP	High-sensitivity C-reactive protein
ICD	International classification of diseases
IVUS	Intravascular ultrasound
LDL-C	Low-density lipoprotein cholesterol
MACE	Major adverse cardiovascular events
MACLE	Major adverse cardiovascular and limb events
MALE	Major adverse limb events
PAD	Peripheral artery disease
PAV	Percent atheroma volume

PCSK9	Protein convertase subtilisin/kexin type 9
SBP	Systolic blood pressure
SGLT2	Sodium-glucose cotransporter 2
TAV	Total atheroma volume

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

1.1. Peripheral artery disease introduction

1.1.1. Introduction

Peripheral artery disease (PAD) is the third most prevalent atherosclerotic disorder following coronary artery and cerebrovascular disease [1]. There are 237 million PAD cases reported worldwide, including 74 million people in the Western Pacific Region. In high-income countries, 7% of adults of age 25 years and above are affected. The incidence increases in older populations and is 21% for people of age 80 to 85 [2]. PAD is characterised by the accumulation of fatty plaque within the arterial vessels supplying the lower extremities [3]. Clinical presentations can vary from silent disease, stable intermittent claudication or atypical symptoms, to acute or chronic limb-threatening ischaemia [4, 5]. Irrespective of how it manifests clinically, PAD has a consistent link with increased mortality and with other cardiovascular conditions [3]. Major adverse cardiovascular events (MACE) is a composite endpoint used in research, which can include myocardial infarction, stroke, and associated mortality. Individuals with PAD have a 2-6-fold higher risk of MACE, compared to age-matched persons in the general population [6]. Only 20-30% of affected people die from non-cardiovascular causes, indicating the importance of secondary prevention [7]. Despite these issues, PAD remains under-diagnosed [8, 9], under-treated [10-12], less well known [8, 13, 14], and less well researched than coronary artery disease and stroke [1, 2]. This introductory chapter outlines the risk factors, the natural history, the evidence for medical and lifestyle treatments, and the current gaps in the literature concerning PAD.

1.1.2. Cardiovascular risk factors and PAD

A prior meta-analysis evaluated how risk factors correlate with the prevalence of PAD in high-income countries. A summary of these associations were as followed: age (per 10-year increase, odds ratio [OR] 1.65, 95% confidence interval [CI], 1.37 to 1.97), current smoking (OR 3.43, 95% CI, 2.58 to 4.58), former smoking (OR 1.94, 95% CI, 1.62 to 2.32), diabetes (OR 1.98, 95% CI, 1.77 to 2.22), hypertension (OR 1.59, 95% CI, 1.46 to 1.74), hypercholesterolaemia (OR 1.43, 95% CI, 1.18 to 1.74), elevated low-density lipoprotein cholesterol (LDL-C) (OR 1.56, 95% CI, 0.79 to 3.10), low high-density lipoprotein cholesterol (HDL-C) (OR 1.84, 95% CI 0.98 to 3.44), elevated triglycerides (OR 1.48, 95% CI, 1.17 to 1.87), body mass index ≥30 kg/m^2 (OR 1.07, 95% CI, 0.64 to 1.79), renal impairment (OR 1.79, 95% CI 1.03 to 3.12), high sensitivity C-reactive protein >3.0 mg/L (OR 2.2, 95% CI, 1.44 to 3.36) [2]. While this meta-analysis did not identify a significant link between low HDL-C and PAD, this relationship was evident in other prospective observational studies [15].

The role of cardiovascular risk factors in PAD differ from other atherosclerotic conditions [16]. Smoking appears to have a more substantial impact in PAD pathogenesis, whereas the effects of hypertension and elevated LDL-C, correlate less, than with coronary artery disease [1, 17].

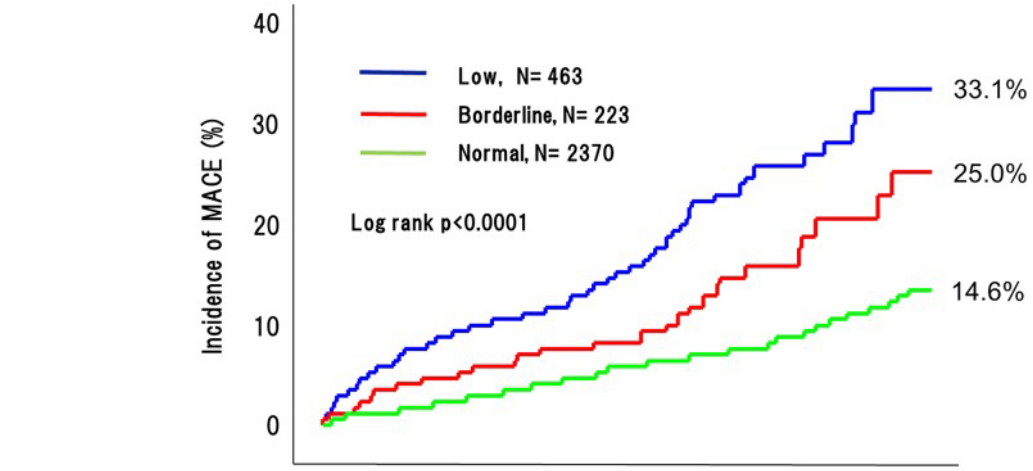
1.2. The natural history of PAD

1.2.1. Abnormal ankle-brachial index

The early stages of PAD are often under-diagnosed, as symptoms can be atypical or absent [4, 18]. An ankle-brachial index (ABI) is a simple and accurate test that can detect PAD before the onset of symptoms [19]. This test involves measurements of the ankle and brachial systolic blood pressures using a handheld Doppler device. The ankle blood pressure is taken over the posterior tibial and dorsalis pedis artery, with the patient in a prone position. An ABI ≤ 0.9 is abnormal, and 0.9 <ABI <1.0 borderline-abnormal for PAD in the tested leg. An ABI >1.4 suggests the lower limb artery is non-compressible, which occurs with PAD that is heavily calcified [19].

Population studies have shown that abnormalities of ABI correspond with an increased risk of MACE, cardiovascular-related mortality and all-cause mortality [20, 21]. A cohort of 4,393 American Indians underwent bilateral ABI testing and then followed for 8.3 years. A U-shaped relationship was observed between mortality and ABI. Low ABI was associated with a multivariate-adjusted increase in all-cause mortality (hazard ratio [HR] 1.69, 95% CI, 1.34 to 2.14) and cardiovascular-related mortality (HR 2.52, 95% CI, 1.74 to 3.64), compared with normal ABI. Likewise, a high ABI correlated with an adjusted increase in all-cause mortality (HR 1.77, 95% CI, 1.48 to 2.13) and cardiovascular-related mortality (HR 2.09, 95% CI, 1.49 to 2.94), in comparison with normal ABI. [22]. Similarly, a study of 3,131 patients with cardiovascular-related hospital presentations, ABI screening was performed, and these cases were followed for 4.8 years. When adjusting for cardiovascular risk factors, low and borderline ABI was associated with a higher risk of MACE (HR 1.93; 95% CI, 1.44 to 2.59; HR 1.54; 95% CI, 1.03 to 2.29, respectively) (Figure 1.1) [23].

Figure 1.1: Kaplan-Meier curve for major adverse cardiovascular events according to ABI classification



Follow up (years)		0	2	4	6	8
Low group	at risk	463	327	198	97	41
	%		9.5	14.2	22.9	31.1
Borderline group	at risk	223	186	129	80	37
	%		5.4	8.3	14.7	20.2
Normal group	at risk	2370	2020	1394	919	390
	%		2.4	5.3	7.6	11.7

Reproduced from Miura T, Minamisawa M, Ueki Y, Abe N, Nishimura H, Hashizume N, et al. 2017. Impressive predictive value of ankle-brachial index for very long-term outcomes in patients with cardiovascular disease: IMPACT-ABI study. PLoS ONE 12(6): e0177609. https://doi.org/10.1371/journal.pone.0177609. Copyright © Miura et al. 2017. Open access article under the terms of the Creative Commons Attribution License [23].

MACE was a composite endpoint of cardiovascular-related mortality, myocardial infarction, and stroke.

1.2.2. Intermittent claudication

Intermittent claudication is a typical manifestation of PAD, described as an exertional lower limb pain of the posterior calf and anterior thigh region. This pain usually restricts walking and resolves within minutes of rest [4]. It is estimated that 10-20% of people with PAD experience intermittent claudication, while an additional 50% have atypical leg symptoms [8, 9]. Symptoms of intermittent claudication can remain stable, although these patients are at high risk of MACE and mortality [24]. Where the condition is treated conservatively, the likelihood of progression to critical limb ischaemia is considered low [25, 26]. In an observational study of 1,107 patients with de novo intermittent claudication, some individuals were initially managed conservatively (37.8%) while others underwent lower extremity revascularisation (63.1%). The 5-year incidence of adverse outcomes for the entire cohort was as follows: minor amputation (0.6%), major amputation (0.2%), critical limb ischaemia (1.1%), worsening claudication (14.8%), MACE (36.9%), cardiovascular-related mortality (14.4%), and all-cause mortality (26.7%). Where major amputation was at the ankle level or above, and minor amputation was below the ankle [24].

1.2.3. Lower extremity revascularisation

For patients with intermittent claudication, lower extremity revascularisation has been shown to improve walking and pain symptoms. In more advanced disease, revascularisation can enhance wound healing and limb salvageability [19]. Despite these potential benefits, this procedure is associated with a high risk of complications. Traditionally, revascularisation was achieved with open surgical repair where lower extremity disease is removed by endarterectomy or bypassed using an autogenous vein or prosthetic graft. In more recent times, endovascular repair consisting of balloon dilatation, stent insertion, and atherectomy has rapidly gained dominance as the preferred revascularisation procedure, although which of these

strategies leads to optimal patient outcomes is unclear [27]. One US study of 381,415 patients undergoing peripheral artery revascularisation, the 1-year incidence of adverse outcomes were as follows: outpatient endovascular reintervention (11.0%), major amputation (3.5%), acute limb ischaemia (6.0%), inpatient surgical reintervention (6.0%), inpatient endovascular reintervention (12.8%), acute unplanned rehospitalisation (38.9%), cardiovascular-related hospitalisation (12.8%), myocardial infarction (2.0%), and stroke (1.0%) [28].

1.2.4. Major adverse limb events

Critical limb ischaemia (CLI) is characterised by severe circulatory disruption complicated by rest pain, skin ulceration, gangrenous infection, or the need for a lower extremity amputation [29]. For the initial treatment of CLI, 25% of individuals undergo primary amputation, 25% have medical treatment-only, and 50% have peripheral artery revascularisation. The one-year prognosis of CLI has been reported as resolving in 25%, continuing in 20%, progressing to amputation in 30%, and leading to death in 25% [7].

Acute limb ischaemia is a sudden thrombotic or embolic occlusion of the peripheral artery. Treatment is urgently required, and the 30-day amputation rate is 10-30% [7]. The rates of mortality following major amputation are very high, reported as 48% after one year, 61% at two years, and 71% at three years [30]. Of the individuals that undergo a below-knee amputation, 40% are fully mobile, 15% have a contralateral amputation, 15% have an above-knee amputation, and 30% die after two years [7].

Major adverse limb events (MALE) are a composite of clinical endpoints that may include CLI, acute limb ischaemia and lower extremity amputation. The COMPASS study examined the natural history of 128 PAD patients that experienced MALE and compared their outcomes with 6,263 unaffected PAD participants. Individuals that experienced MALE had

higher rates of cardiovascular-related hospitalisation (adjusted HR 11.7, $p<0.0001$), MACE or vascular amputation (adjusted HR 7.6, $p<0.0001$), and all-cause mortality (adjusted HR 3.2, $p<0.0001$), compared to those unaffected with MALE [31]. The natural history of PAD, according to different clinical presentations, is summarised in Table 1.1.

Table 1.1: The natural history of PAD according to clinical presentations

Clinical presentation	Borderline ABI and CV-hospitalisation [23]	Abnormal ABI and CV-hospitalisation [23]	De novo intermittent claudication [24]	Peripheral artery revascularisation [28]	MALE† [31]	Major amputation [30]
Study follow-up	8 years	8 years	5 years	1 year	1 year	1 year
1-Year event-rate*						
Mortality	-	-	5.3%	-	8.3%	48.3%
CV-mortality	2.3%	3.3%	2.9%	-	-	-
MACE	3.1%	4.1%	7.4%	-	3.7%	-
MI	-	-	-	2.0%	-	5.0%
Stroke	-	-	-	1.0%	-	4.3%
CV-hospitalisation	-	-	-	12.8%	57.6%	-
MALE	-	-	-	10.3%	-	-
Major amputation	-	-	0.04%	3.5%	20.5%	-
CLI	-	-	0.2%	-	-	-
ALI	-	-	-	2.6%	-	-

*MACE definitions differed across studies. *The 1-year event-rate was estimated from the total events during follow-up in the studies cited. †These outcomes were reported from a clinical trial, whereby one-third of participants received treatment that significantly reduced MACE and MALE. Therefore, they could have been lower-risk than in real-world settings. Abbreviations: ABI, ankle-brachial index; ALI, acute limb ischaemia; CLI, critical limb ischaemia; CV, cardiovascular; MACE, major adverse cardiovascular events; MALE, major adverse limb events; MI, myocardial infarction.*

1.3. Medical and lifestyle management of PAD

1.3.1. Smoking cessation

Smoking is a modifiable risk factor that progressively contributes to limb morbidity and MACE [32]. One study reviewed 739 consecutive patients undergoing peripheral angiography for claudication or critical limb ischaemia over a 5-year duration. In the 30% of patients that ceased smoking during follow-up, there was a lesser incidence of amputation and mortality, compared with individuals that had continued to smoke [33]. For another group of patients undergoing infra-inguinal bypass surgery, active smoking correlated with early graft failure after multivariate analysis (adjusted odds ratio 1.21, 95% confidence interval [CI], 1.02 to 1.43) [34]. Cessation of smoking is an essential treatment for intermittent claudication, associated with improved walking performance and less pain. It was demonstrated that participants with symptomatic PAD that abstained smoking could achieve a greater maximum treadmill walking distance, compared with ongoing smokers, when they were reviewed after ten months [35].

Clinicians should routinely offer counselling and pharmacotherapy, as these have been shown to improve the success of smoking abstinence [19]. One study randomised 124 participants with a history of smoking and PAD to intensive counselling intervention or standard care. At six months, abstinence from smoking was higher in the intensive group (21.3%), compared with standard care (6.8%) [36].

There is evidence for safety and efficacy of pharmacotherapy (varenicline, bupropion and nicotine replacement therapy) when added to supportive counselling [37-39]. These treatments have been extensively studied in the broader population. A Cochrane review collated data from 150 trials inclusive of more than 50,000 study participants in randomised controlled trials of nicotine replacement. All available forms of nicotine replacement (gum, transdermal patch, nasal spray, inhaler and sublingual tablets) were found to be more effective

than placebo in achieving smoking abstinence, irrespective of the setting (relative risk reduction 1.60, 95% CI, 1.53 to 1.68). Further benefit can be derived from combining different forms of nicotine replacement (such as patch and gum), compared to the use of a single type. Also, the addition of nicotine replacement therapy to bupropion was more effective than bupropion alone [40]. Varenicline, a partial nicotinic acetylcholine receptor agonist, was tested in patients with known cardiovascular disease. There were 714 participants, including 179 people (25.1%) with PAD, that received smoking-cessation with varenicline (1mg twice daily) or placebo for 12 weeks. Varenicline appeared safe and was more effective than placebo, with an uninterrupted abstinence rate between weeks 9 to 52 (19.2% versus 7.2%, $p<0.0001$) [38].

Recommendation: Smoking cessation counselling and pharmacotherapy (nicotine replacement therapy, bupropion, or varenicline) is strongly recommended.

1.3.2. Exercise therapy

Regular physical activity is inversely correlated with the risk of mortality in people with PAD [41]. Exercise is the most effective non-invasive therapy for symptoms of intermittent claudication. The American Heart Association recommends a supervised exercise program comprising at least three walking sessions per week (30 to 60 min each) for a minimum duration of 12 weeks [19]. A systematic review evaluated the effect of supervised walking therapy on ambulation, with a pool of 25 randomised controlled trials and 1,054 participants having intermittent claudication. Supervised walking therapy was associated with an increase in maximum walk distance (180 metres, 95% CI, 130 to 340 metres) and pain-free walk distance (128 metres, 95% CI, 92 to 165 metres), compared with non-intervention [42]. Comparisons

have been made between supervised and unsupervised training. A meta-analysis combined 14 PAD studies, where these interventions were directly compared. Unsupervised exercise differed between these studies and included walking advice and home-based programs. Supervised exercise therapy led to significant improvement in maximal walking and pain-free walking distance at 12-months, compared with unsupervised training. The maximal walk distance increase amounted to 180 metres, but there was no significant effect on the quality of life scores. The authors of this meta-analysis suggested that direct supervision might enhance the workload and adherence to training, although this has not been conclusively proven [43].

Supervised exercise therapy is recommended as an initial treatment for intermittent claudication before consideration for lower limb revascularisation [19]. The CLEVER study randomly divided patients with aortoiliac disease into three groups: control, supervised exercise therapy and stent revascularisation; all receiving optimal medical therapy. From baseline to 18 months, both interventions improved peak walk time and quality of life scores, compared with control. There was no significant difference in peak walk time between supervised exercise and stent revascularisation. There was a demonstrable increase of claudication onset time for supervised exercise but not for stent revascularisation, in comparison with control. Overall, the CLEVER study established exercise as a viable initial treatment for intermittent claudication [44]. The combination of revascularisation and supervised exercise therapy could be more effective than either treatment alone. In a meta-analysis, which included eight clinical trials, combined therapy led to a favourable increase in the maximal walk (mean difference [MD] range 82 to 321 metres) and pain-free walk distance (MD range 38 to 408 metres), compared with revascularisation or supervised training alone [45]. However, supervised exercise therapy is usually the initially preferred, as revascularisation is often associated with procedural risks, and long-term outcomes have not been well characterised [19, 28].

Supervised exercise therapy is safe for most patients with PAD, but implementation can be challenging. Cardiovascular disease, lower limb rest pain, ulceration or amputation and other medical comorbidities can restrict the ability to exercise [46]. One study examined the participation of 201 patients with stable claudication at three physical rehabilitation centres. Physical contraindications significantly limited approximately one-third of people. An additional third of the cohort was unable to attend, with transport and time issues commonly being reported [47]. While studies of supervised exercise have been mostly walking-based, there are other possibilities, including cycling, strength training and arm-cranking. These could be useful when a walking-based program is not feasible. One review found no significant differences in the benefits of supervised walking and other training methods. Both interventions improved the quality of life scores. More evidence is needed to clarify the differences in these training methods [48].

Transportation options can limit supervised exercise therapy at facilities [49]. There is increasing attention to alternative structured exercise programs, that require less travelling to centres. Structured community or home-based exercise programs utilise clinician-supported and instruction-based techniques. A clinical study of 180 patients examined the effect of a step-monitored home exercise program on walking. Participants with mild-to-moderate severity intermittent claudication were randomised to step-monitored home exercise, supervised exercise or the control group for 12 weeks. The step-monitored home exercise was comparable to supervised training, with regards to walking performance and participant compliance [50].

Recommendation: Supervised exercise therapy is recommended for intermittent claudication, wherever practical. Home- and community- based exercise programs can be implemented as an alternative.

1.3.3. Antiplatelet therapy

The American Heart Association recommends antiplatelet monotherapy for all patients with symptomatic PAD [19]. In a previous meta-analysis, aspirin monotherapy was associated with a reduction in stroke (HR 0.64, 95% CI, 0.42 to 0.99), but no significant difference in major adverse cardiovascular events, cardiovascular mortality, myocardial infarction or major bleeding, compared with placebo. However, differences might have been observed in these studies if they were more extensive [51]. The CAPRIE study compared the relative efficacy of clopidogrel (75mg daily) and aspirin (325mg daily) in reducing MACE (composite of cardiovascular mortality, myocardial infarction and stroke). Of the total 19,185 participants, there was a cohort of 6,452 (33.6%) persons classified as having symptomatic PAD. In this subgroup, clopidogrel was associated with a 23.8% relative risk reduction in MACE compared to aspirin. Both treatments had comparable rates of major bleeding [52]. While clopidogrel was more efficacious than aspirin in the CAPRIE study, the American Heart Association does not have a preference. Also, dual antiplatelet therapy for people with intermittent claudication is not usually recommended [19]. The CHARISMA trial randomised 15,603 patients with stable atherosclerotic disease (or multiple cardiovascular risk factors) to aspirin and clopidogrel combination or aspirin monotherapy. In a post hoc analysis of 3,096 participants with PAD, there was no difference between dual antiplatelet therapy and aspirin alone in MACE (composite of myocardial infarction, stroke and cardiovascular mortality), stroke, all-cause mortality or severe bleeding. Among other secondary endpoints, combination therapy reduced myocardial infarction (HR 0.63, 95% CI, 0.42 to 0.96), and rate of hospitalisation for ischaemic events (HR 0.81, 95% CI, 0.68 to 0.95), but was associated with increased minor bleeding (HR 1.99, 95% CI, 1.69 to 2.34) [53] (outlined in Table 1.2).

There is some evidence for prescribing dual antiplatelet therapy following lower limb revascularisation, although the relevant studies were too small to evaluate cardiovascular

outcomes. One randomised controlled trial of 80 participants found that dual antiplatelet therapy was associated with lower disease restenosis and target revascularisation following elective femoropopliteal angioplasty, compared with aspirin alone. However, these benefits did not extend to one year, where clopidogrel was ceased at six months. Therefore, prolonged dual antiplatelet therapy (> 6months) should be considered for patients who are deemed at high risk of restenosis [54]. In another study, the addition of clopidogrel to aspirin significantly improved limb outcomes in the subgroup undergoing below-knee prosthetic graft operation, but not those receiving a venous graft [55].

Alternative antiplatelet therapy has been evaluated in patients with symptomatic PAD. Ticagrelor is a $P2Y_{12}$ inhibitor, indicated for acute coronary syndrome [56]. The EUCLID study randomised 13,885 patients with symptomatic PAD to ticagrelor (90mg twice daily) or clopidogrel (75mg daily). There was no significant difference between groups in MACE, acute limb ischaemia, or major bleeding [57] (outlined in Table 1.3).

Recommendation: Clopidogrel is preferable to aspirin monotherapy for all patients. Prolonged dual antiplatelet therapy (> 6months) should be considered following revascularisation in those at high risk of restenosis. The evidence for the use of dual antiplatelet therapy to reduce MACE is lacking, although clinicians should follow relevant guidelines when there is co-existent coronary artery disease.

1.3.4. Anticoagulant therapy

Warfarin, unfractionated heparin and low-molecular-weight heparin have not been demonstrated to reduce ischaemic events, and they increase bleeding risk when compared with antiplatelet monotherapy [58]. The WAVE trial randomised 2,161 patients with PAD to an

antiplatelet alone or the combination of an antiplatelet with warfarin (target international normalised ratio [INR] 2.0 to 3.0). Combined antithrombotics did not reduce MACE, and there was an increase in life-threatening bleeding (HR 3.41, 95% CI, 1.84 to 6.35) [59]. The BOA trial compared warfarin (INR target 3.0 to 4.5) with aspirin alone in 2,690 patients that underwent an infrainguinal bypass operation. There was no difference in the rate of MACE or graft occlusion, and anticoagulation was associated with higher bleeding events [60]. In the absence of another indication, these anticoagulants are not recommended in patients with PAD [19].

While current guidelines recommend antiplatelet monotherapy to reduce the risk of MACE and major adverse limb events in PAD [19, 61], these could be revised, in light of more recent evidence. Rivaroxaban is a direct-acting anticoagulant which has been researched in stable and unstable cardiovascular presentations [31, 62, 63]. ATLAS ACS 2-TIMI 51 was a randomised controlled trial that investigated the effect of additional rivaroxaban to standard antiplatelet therapy immediately following an acute coronary syndrome. A total of 15,526 patients were randomised to rivaroxaban 2.5mg twice daily, 5mg twice daily or placebo for a mean of 13 months and up to 31 months. Rivaroxaban (pooled doses) was associated with reduced major adverse cardiovascular events (HR 0.84, 95% CI, 0.74 to 0.96), increased risk of major bleeding (HR 3.96, 95% CI, 2.46 to 6.38) and intracranial haemorrhage (HR 3.28, 95% CI, 1.28 to 8.42), but not fatal bleeding (HR 1.19, 95% CI, 0.54 to 2.59, p=0.66) [62]. Excessive major bleeding has precluded rivaroxaban from being recommended for acute coronary syndrome management.

COMPASS was a randomised controlled trial that investigated MACE and limb outcomes in 27,395 people with stable atherosclerotic vascular disease, including 6,391 persons with PAD. Participants were randomised to three groups, rivaroxaban alone (5mg twice daily), the combination of rivaroxaban (2.5mg twice daily) plus aspirin (100mg daily) or

aspirin alone (100mg daily). The PAD subgroup appeared to benefit more than the other high-risk participants [31, 63, 64]. Combined low-dose rivaroxaban and aspirin was associated with a reduction in MACE (HR 0.67, 95% CI, 0.52 to 0.87) [63], major adverse limb events (HR 0.57, 95% CI, 0.37 to 0.88), and major amputation (HR 0.33, 95% CI, 0.12 to 0.92), at the expense of increased major bleeding (HR 1.60, 95% CI, 1.09 to 2.36), compared with aspirin alone [31]. Of note, COMPASS recruited people with stable PAD, where the risk of major adverse cardiovascular and limb events is significantly less than with critical limb ischaemia [24, 31]. The reduction in MACE was driven predominantly by fewer ischaemic stroke [63]. It could be argued that combined low-dose rivaroxaban and aspirin had a modest absolute reduction in stroke and major adverse limb events, compared to aspirin alone (approximately 1.0% and 1.1%, respectively) [31, 63]. Therefore, when prescribing combined low-dose rivaroxaban and aspirin, the net benefit of MACE and major adverse limb events needs to be weighed against the risk of major bleeding. In COMPASS, rivaroxaban alone did not improve cardiovascular or limb outcomes and was associated with increased major bleeding, compared to aspirin alone [63].

Patients presenting with critical limb ischaemia have a high risk of subsequent MACE and major adverse limb events [31]. Critical limb ischaemia leads to amputation in 10-40% of presentations, and this is a contributor to permanent disability and exceptionally high mortality rates, estimated at 40-70% within five years [6]. Few studies have investigated antithrombotic use in this setting to guide clinical practice. Likewise, lower extremity revascularisation is another clinical driver of MACE and major adverse limb events [28, 31]. The EPAD study compared edoxaban with clopidogrel, in addition to aspirin in 203 participants following a femoropopliteal endovascular intervention. This was a proof-of-concept study, which suggested edoxaban could be associated with lower bleeding and restenosis or occlusion, in comparison with clopidogrel [65]. VOYAGER PAD is an upcoming cardiovascular outcome

study. A total of 6,500 participants are being randomised to rivaroxaban 2.5mg twice daily or placebo following lower extremity revascularisation [66].

Recommendation: In patients at high risk of ischaemic cardiovascular or lower limb events, where bleeding risks are low, a combination of low-dose rivaroxaban and aspirin should be considered.

1.3.5. Antihypertensive therapy

Treatment of hypertension reduces the risk of MACE in the general population [67]. In one meta-analysis, patients with a higher baseline cardiovascular risk that were treated with antihypertensive therapy had a greater absolute risk reduction [68]. Few of these studies specifically included people with PAD. The HOPE study was a randomised controlled trial where ramipril therapy in the PAD cohort led to a 22% relative risk reduction in major adverse cardiovascular events [69]. ON TARGET (Ongoing telmisartan alone and in combination with ramipril global endpoint trial) included 3,468 patients with PAD. The study generally found no difference in MACE (composite endpoint of cardiovascular-related mortality, myocardial infarction, stroke or hospitalisation for heart failure) between the telmisartan and ramipril therapy groups, indicating they have comparable benefits [70]. Angiotensin-converting enzyme (ACE) inhibitors can improve walking performance in patients with symptomatic PAD. One meta-analysis, which pooled six randomised controlled trials found that ACE inhibitors were associated with an increase in maximum walk distance and pain-free walk distance, compared with placebo [71]. Overall, ACE inhibitors or angiotensin-2 receptor blockers may be preferred antihypertensives, as they may have potential additional benefits. Beta-blockers are considered safe, despite theoretical concerns that this can exacerbate lower

extremity ischaemia [72]. Treatment-resistant hypertension is a condition that shares many risk factors with PAD, including older age, renal impairment and diabetes [73]. In a previous single-centre study of 491 patients undergoing lower extremity angiography for PAD, renal artery stenosis was evident in 26% [74]. Given the high prevalence of these comorbidities among PAD patients, at least two antihypertensive agents are usually required [7, 75].

The ideal blood pressure target for high-risk patients has been a point of contention [76-80]. Lowering blood pressure to below 140/90 mmHg was the standard recommendation [81]. The ACCORD BP study found no cardiovascular benefit of more intensive control (target systolic blood pressure <120 mmHg) in patients in type 2 diabetes, compared with standard control (target systolic blood pressure <140 mmHg). Intensive therapy was also associated with a higher incidence of severe adverse events, including hypotension, syncope, bradycardia, hyperkalaemia, and acute kidney injury [82]. Subsequently, a meta-analysis evaluated cardiovascular outcomes from 31 antihypertensive intervention studies in patients with diabetes. More intensive blood pressure reduction was associated with a 9% lower incidence of stroke, compared with lower intensity therapy. For each 5-mmHg reduction in systolic blood pressure, the risk of stroke decreased by 13%. However, there was no association between the extent of blood pressure reduction and the risk of myocardial infarction [83].

SPRINT examined hypertension management in patients without diabetes and had similar blood pressure goals to ACCORD BP. Intensive treatment reduced the incidence of the MACE, compared with standard treatment (HR 0.75, 95% CI, 0.64 to 0.89), at the expense of increased incidence of severe adverse events. While SPRINT did demonstrate the efficacy of intensive blood pressure control, there are concerns with how these findings can be extrapolated to different populations. This study did not specifically investigate PAD, and people with diabetes, end-stage renal disease, age of 75 years or older or prior stroke were excluded [84]. Therefore, it could be argued that patients of a higher complexity were not

evaluated. These types of patients might be more susceptible to the side effects of blood pressure-lowering [85]. Worsening renal function is an adverse event that is especially relevant for people with existing chronic kidney disease. The subgroup of SPRINT with stage 3 to 4 chronic kidney disease (estimated glomerular filtration rate [GFR] between 20 and 60 ml/min/1.73 m^2) did appear to benefit from intensive blood pressure control. Nevertheless, blood pressure reduction in chronic kidney disease should be performed gradually and with caution, given the risk of worsening GFR and electrolyte abnormalities [73].

Dizziness and other side effects from intensive blood pressure reduction can limit treatment adherence. Some factors affecting compliance include increasing age (≥80 years), previous non-adherence, side effects, presence of multiple medical comorbidities, polypharmacy and excessive cost burden [75]. Many experts advocate for a more individualised blood pressure target in elderly patients, with the aid of frailty-defining scores [85]. Overall, it is reasonable for the clinician to treat hypertension intensively (target systolic blood pressure of 120 mmHg) for patients with PAD, in the absence of risk factors associated with safety and non-adherence.

Recommendation: It is reasonable to treat hypertension intensively (systolic blood pressure goal of 120 mmHg), where it is perceived to be safe and well-tolerated. Otherwise, treat with a more conservative target (blood pressure <140/90 mmHg). Generally, the preference is for ACE inhibitors or angiotensin-2 receptor blockers as first-line therapy.

1.3.6. Lipid-lowering therapy

Statins are clinically indicated for all patients with PAD, regardless of lipid levels [19]. In the Heart Protection Study 20,436 high-risk participants, including 6,748 with PAD, were randomised to receive simvastatin 40mg daily or placebo. Simvastatin in the PAD subgroup was associated with a 22% relative risk reduction in the incidence of MACE. The observed risk reduction for participants with a baseline total cholesterol less than 5.0 mmol/L or low-density lipoprotein cholesterol (LDL-C) less than 3.0 mmol/L was comparable to those with more elevated lipids [86]. The REACH registry found that statin therapy was associated with less cardiovascular and limb events. Of the total 68,236 participants enrolled, there was a cohort of 5,861 patients with symptomatic PAD prospectively followed for four years. In a multivariate analysis, patients on statins at baseline (62.2%) were compared with those who were not (37.8%). Statin therapy was associated with a reduced composite of adverse limb events (HR 0.82, 95% CI, 0.72 to 0.95) and MACE (HR 0.83, 95% CI, 0.73 to 0.96). Specifically, patients on statins had a lower incidence of worsening claudication or development of new critical ischaemia, new lower extremity percutaneous or surgical revascularisation, and new ischaemic amputation, compared with those who were not [87]. High-intensity statin therapy is preferable. In one meta-analysis that pooled 39,612 participants from secondary prevention studies, high-intensity statin was associated with a 15% relative risk reduction in major vascular events, compared with low-intensity therapy. This MACE benefit correlated with the level of LDL-C reduction across all studied patient types, even those with an LDL-C less than 2 mmol/L. Overall, a lowering of LDL-C by 2-3 mmol/L approximated to a 40-50% risk reduction [88]. In a study of 909 PAD patients that underwent peripheral angiography, high-intensity statin use was associated with improved survival (HR 0.52, 95% CI, 0.33 to 0.81) and lesser MACE (HR 0.58, 95% CI, 0.37 to 0.92), compared with a lower-intensity statin. This divergence in outcomes was observed despite the group similarities in demographics, mean LDL-C level,

and other cardiovascular risk factors [89]. Statins also improved walking performance and pain symptoms in small randomised controlled trials of patients with intermittent claudication [90, 91]. In one study, 69 participants with symptomatic PAD were randomised to simvastatin 40mg/day or placebo for one year. The simvastatin group had a more prolonged treadmill exercise time until claudication of 54 seconds (24% increase) and 94 seconds (42% increase) when studied at 6 and 12 months respectively [90].

There is evidence for other LDL-C lowering therapies, including ezetimibe and protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in high-risk populations [92]. In the FOURIER study, there were 3,642 patients with PAD that were randomised to receive evolocumab (PCSK9 inhibitor) or placebo. For PAD patients treated with evolocumab, there was significant relative risk reduction in MACE (HR 0.79, 95% CI, 0.66 to 0.94), but not for major adverse limb events (HR 0.63, 95% CI, 0.39 to 1.03). However, in all 27,564 participants, evolocumab was associated with reduced major adverse limb events (HR 0.58, 95% CI, 0.38 to 0.88). There was a linear correlation between LDL-C reduction and lesser limb events that continued even to levels below 10 mg/dL (0.26 mmol/L) [93]. PCSK9 inhibitors are not commonly used at this time. Some caveats include a lack of long-term safety data, as well as some economic considerations [94]. Lipid targets are recommended to guide the prescription of non-statin treatments. For individuals on maximally tolerated statin therapy, it is reasonable to add ezetimibe or PCSK9 inhibitors with a goal of a ≥50% LDL-C reduction, or LDL-C <1.8 mmol/L and non-high-density lipoprotein cholesterol (non-HDL-C) <2.6 mmol/L. Ezetimibe is a commonly prescribed LDL-C lowering treatment that is currently more accessible than PCSK9 inhibitors [92]. The clinician should also consider additional risk factors that warrant intensive lipid-lowering including age ≥65 years, prior myocardial infarction or ischaemic stroke, current smoking, history of coronary revascularisation or

residual multi-vessel coronary artery disease, metabolic syndrome or high sensitivity C-reactive protein >2mg/L [92, 94].

Recommendation: Maximally tolerated statins are recommended for all patients, irrespective of lipid levels. Consider the addition of ezetimibe or PCSK9 inhibitors to achieve a goal of ≥50% LDL-C reduction, or LDL-C <1.8 mmol/L and non-HDL-C <2.6 mmol/L.

1.3.7. Glycaemic control in diabetes

The benefit of intensive glycaemic control for patients with diabetes and PAD is unclear. Diabetes is a major risk factor for cardiovascular disease and PAD [95]. The duration and degree of hyperglycaemia have been linked with disease burden. In the UKPDS, each 1% increase in glycated haemoglobin was associated with a 28% increased incidence of PAD, independent of other risk factors [96]. Individuals affected with PAD and diabetes are more likely experience aggressive manifestations of the disease, such as worsening lower extremity function, sudden arterial thrombosis, and ischaemic ulceration, compared to those with PAD alone [97]. This pathophysiology contributes between 5- to 10-fold increased likelihood of major lower limb amputation [7]. Small observational studies have examined clinical outcomes in patients with diabetes undergoing lower extremity revascularisation. Poor glycaemic control correlated with decreased arterial patency rates and increased risk of major adverse limb events [98, 99]. A post hoc analysis of patients with diabetes and PAD in the EUCLID trial showed that every 1% increase in HbA1c, was associated with a 14% increased relative risk for MACE [100]. However, intensive glycaemic control in patients with established atherosclerotic cardiovascular disease has not been shown to improve cardiovascular outcomes in randomised

clinical trials. One meta-analysis pooled four large randomised controlled trials, comparing intensive and standard glycaemic control in patients with diabetes. Intensive therapy led to a mean reduction of HbA1c by 0.88% at the final visit, and a 9% relative risk reduction (95% CI, 1-16%) of major adverse cardiovascular events, compared with standard therapy. However, for the subgroup with a history of vascular disease, intensive glycaemic control did not significantly improve macrovascular outcomes. Also, intensive therapy for all participants was associated with an increased incidence of severe hypoglycaemia (HR 2.48, 95% CI, 1.91 to 3.21), compared with standard therapy [101]. Another meta-analysis examined the effect of tight glycaemic control for patients with diabetes on microvascular complications. Intensive therapy reduced renal events (HR 0.80, 95% CI, 0.72 to 0.88), and there was a trend towards lesser ophthalmic events (HR 0.87, 95% CI, 0.76 to 1.00). There was no reduction in neuropathy with intensive-treatment in comparison with standard therapy, although assessment was limited to variable and subjective methods in these studies [102].

The risks of hypoglycaemia should always be considered when setting glycaemic targets. Hypoglycaemia is frequent and under-recognised in the elderly. It is associated with falls, cognitive impairment and hospitalisation. The use of a longer-acting sulfonylurea or an intensive insulin regimen, polypharmacy, renal disease, cognitive impairment, malnutrition and physical frailty all increase the likelihood of hypoglycaemia [103, 104].

Sodium-glucose cotransporter 2 inhibitors (SGLT2) have emerged as new hypoglycaemic agents, with broad metabolic effects. In addition to glycaemic control, they have been associated with a reduction in weight, waist circumference, blood pressure and increases in LDL and HDL cholesterol. In the CANVAS Program study, canagliflozin therapy was associated with a relative risk reduction in MACE (HR 0.86, 95% CI, 0.75 to 0.97), compared with placebo. However, the canagliflozin group had a higher risk of lower limb amputation (HR 1.97, 95% CI, 1.41 to 2.75). Currently, the mechanism and clinical

implications of this finding are unclear [105]. This unexpected safety signal was not evident in studies of other SGLT2 inhibitors. EMPA-REG was a randomised controlled trial of empagliflozin, where 7,020 patients (including 1,461 patients with a history of PAD). Empagliflozin reduced MACE (HR 0.86, 95% CI, 0.74 to 0.99), and this was driven by a 38% relative risk reduction in cardiovascular-related mortality [106]. SGLT2 inhibitors appear to have broad metabolic benefits and reduce major adverse cardiovascular events. Nevertheless, caution would be advised in patients with PAD, given the correlation between canagliflozin therapy and an increased incidence of lower limb amputation. The recommendations for management of PAD is summarised in Table 1.4.

Recommendation: Glycaemic goals should be individualised in patients with diabetes. A target HbA1c <7.0% could be considered, in patients without a high risk of hypoglycaemia.

Table 1.2: Earlier cardiovascular outcome trials

	CHARISMA N = 3,096	**WAVE N = 2,161**	**HOPE N = 4,051**	**HPS N = 6,748**
Treatment	Antiplatelet	Anticoagulation	Hypertension	Dyslipidaemia
Study Type	RCT	RCT	RCT	RCT
Study Group	PAD cohort	Symptomatic PAD or cerebrovascular disease	PAD cohort	Symptomatic PAD cohort and dyslipidaemia
Treatment Groups	(1) Clopidogrel (75mg once daily) and low-dose aspirin (2) Clopidogrel (75mg once daily)	(1) Warfarin (target INR 2.0 to 3.0) and antiplatelet (2) Antiplatelet	(1) Ramipril (10mg once daily) (2) Placebo	(1) Simvastatin (40mg once daily) (2) Placebo
Primary Outcome	3-point MACE	3-point MACE	3-point MACE	3- point MACE
Hazard ratio	0.85 (0.66-1.08)	0.92 (0.73-1.16)	0.78 ($p<0.05$)	0.78 (0.71-0.85)
Secondary Outcomes				
CV Mortality	0.92 (0.65-1.28)	1.04 (0.74-1.46)	-	-
All-Cause Mortality	0.89 (0.68-1.16)	1.04 (0.79-1.38)	-	-
MI	0.63 (0.42-0.96)	0.82 (0.57-1.18)	-	-
Stroke	0.79 (0.51-1.21)	1.01 (0.65-1.59)	-	-
Major Bleeding	0.97 (0.56-1.66)	3.41 (1.84-6.35)	-	-
Minor Bleeding	1.99 (1.69-2.34)	3.63 (3.01-4.38)	-	-

All relative risks are expressed as a hazard ratio (HR) and (95% confidence intervals), with placebo as the reference group. Data is from the following trials: CHARISMA [53], WAVE [59], HOPE [69], HPS [86]. Definitions of MACE are as follows: CHARISMA (CV mortality, MI and stroke); WAVE (CV mortality, MI and stroke); HOPE (CV mortality, MI and stroke); HPS (MI, stroke, coronary or non-coronary revascularisation).

Abbreviations: ACS, acute coronary syndrome; ALI, acute limb ischaemia; BD, twice daily; CV, cardiovascular; HR, hazard ratio; LLA, lower limb amputation; MACE, major adverse cardiovascular events; MI, myocardial infarction; OD, once daily; PAD, peripheral artery disease; RCT, randomised controlled trial, sBP, systolic blood pressure.

Table 1.3: Contemporary cardiovascular outcome trials

	EUCLID N = 13,885	**COMPASS PAD N = 7,470**		**SPRINT N = 9,361**	**FOURIER N = 3,642**	**EMPA-REG N = 1,461**
Treatment	Antiplatelet	Anticoagulation		Hypertension	Dyslipidaemia	Diabetes
Design	RCT	RCT		RCT	RCT	RCT
Cohort	PAD	PAD or carotid disease		Stable CV disease	PAD	PAD and DM
Treatment Groups	(1) Ticagrelor (90mg BD) (2) Clopidogrel (75mg OD)	(1) Rivaroxaban alone (5mg BD) (2) Aspirin alone (100mg OD)	(1) Rivaroxaban (2.5mg BD) and aspirin (100mg OD) (2) Aspirin alone (100mg OD)	(1) Intensive control (sBP< 120mmHg) (2) Standard control (sBP< 140mmHg)	(1) Evolocumab (2) Placebo	(1) Empagliflozin (2) Placebo
Primary Outcome	3-Point MACE	3-Point MACE	3-Point MACE	4-Point MACE	4-Point MACE	4-Point MACE
HR	1.02 (0.92-1.13)	0.86 (0.69-1.08)	0.72 (0.57-0.90)	0.75 (0.64-0.89)	0.79 (0.66-0.94)	0.93 (0.70-1.24)
Secondary Outcomes						
CV Mortality	1.07 (0.92-1.23)	0.86 (0.62-1.19)	0.82 (0.59-1.14)	0.57 (0.38-0.85)	1.02 (0.71-1.48)	0.57 (0.37-0.88)
All-Cause Mortality	0.99 (0.89-1.11)	0.95 (0.75-1.20)	0.91 (0.72-1.16)	0.73 (0.60-0.90)	0.92 (0.69-1.23)	0.62 (0.44-0.88)
MI	1.06 (0.91-1.23)	0.84 (0.59-1.20)	0.76 (0.53-1.09)	0.83 (0.64-1.09)	0.69 (0.52-0.91)	-
Stroke	0.78 (0.62-0.98)	0.93 (0.61-1.40)	0.54 (0.33-0.87)	0.89 (0.63-1.25)	0.59 (0.38-0.92)	-
Major Bleeding	1.10 (0.84-1.43)	1.68 (1.17-2.40)	1.61 (1.12-2.31)	-	-	-
LLA	-	0.46 (0.20-1.08)	0.30 (0.11-0.80)	-	0.41 (0.11–1.57)	0.84 (0.54-1.32)
ALI	1.03 (0.79-1.33)	0.57 (0.32-1.00)	0.56 (0.32-0.99)	-	0.73 (0.37-1.48)	-

All relative risks are expressed as a hazard ratio (HR), with placebo as the reference group. Data is from the following trials: EUCLID [57], COMPASS [31, 63], SPRINT [84], FOURIER [93], EMPA-REG [107]. Definitions of MACE are as follows: EUCLID (CV mortality, MI and ischaemic stroke); COMPASS PAD (CV mortality, MI and stroke); SPRINT (MI, stroke, heart failure and mortality); FOURIER (CV mortality, MI, stroke, and hospitalisation for ACS or coronary revascularisation); EMPA-REG (CV mortality, MI, stroke, and hospitalisation for ACS). Abbreviations as per Table 1.2.

Table 1.4: Summary of recommendations for the management of PAD

	Recommendations in peripheral artery disease
Smoking cessation	Smoking cessation counselling and pharmacotherapy (nicotine replacement therapy, bupropion, or varenicline) is strongly recommended.
Exercise therapy	Supervised exercise therapy is recommended for intermittent claudication, wherever practical. Home- and community- based exercise programs can be implemented as an alternative.
Antiplatelet therapy	Clopidogrel is preferable to aspirin monotherapy for all patients. Prolonged dual antiplatelet therapy (> 6months) should be considered following revascularisation in those at high risk of restenosis. The evidence for the use of dual antiplatelet therapy to reduce MACE is lacking, although clinicians should follow relevant guidelines when there is co-existent coronary artery disease.
Anticoagulant therapy	In patients at high risk of ischaemic events, where bleeding risks are low, a combination of low-dose rivaroxaban and aspirin should be considered.
Antihypertensive therapy	It is reasonable to treat hypertension intensively (systolic blood pressure goal of 120 mmHg), where it is perceived to be safe and well-tolerated. Otherwise, treat with a more conservative target (blood pressure <140/90 mmHg). Generally, the preference is for ACE inhibitors or angiotensin-2 receptor blockers as first-line therapy.
Lipid-lowering therapy	Maximally tolerated statins are recommended for all patients, irrespective of lipid levels. Consider the addition of ezetimibe or PCSK9 inhibitors to achieve a goal of ≥50% LDL-C reduction, or LDL-C <1.8 mmol/L and non-HDL-C <2.6 mmol/L.
Glycaemic control in diabetes	Glycaemic goals should be individualised in patients with diabetes. A target HbA1c <7.0% could be considered, in patients without a high risk of hypoglycaemia.

1.4. Other areas for further investigation in PAD

1.4.1. Critical limb ischaemia management

Critical limb ischaemia (CLI) is characterised by a significant disruption in limb perfusion, which can be complicated by rest pain, ulceration, gangrenous infection, and could necessitate a lower extremity amputation [7]. Management of CLI is distinct from earlier stages of PAD. For intermittent claudication, the emphasis is usually to provide non-invasive treatments, whereas, in CLI, there is a greater dependency on lower extremity intervention [7, 28]. The consequences of delayed diagnosis can be devastating, as the salvageability of a lower limb can depend on the timeliness of revascularisation and wound care [108, 109]. Traditionally, revascularisation was achieved with open surgical repair where lower extremity disease is removed by endarterectomy or bypassed using an autogenous vein or prosthetic graft. In more recent times, endovascular repair consisting of balloon dilatation, and stent insertion has gained dominance as the preferred revascularisation procedure, although which of these strategies leads to optimal long-term patient outcomes is unclear [19].

A diverse and well-connected team approach is required to cater for a variety of patient needs [29]. One single-centre study compared outcomes of standard care with multidisciplinary care in 146 consecutive cases of CLI. Standard care was defined as input from different medical providers, without an appointed case manager or a system for open communication and referral. Multidisciplinary care featured regular collaborations between vascular, plastic and podiatry surgeons, and further consultation from infectious disease, internal medicine and cardiology specialists. The investigators of this study described an inefficiency and lack of medical continuity with the standard approach. Multidisciplinary care was associated with a two-fold improvement in amputation-free survival [110].

CLI is associated with very high rates of MACE and mortality, although the evidence for risk factor control is limited [19]. CLI is associated with frailty and renal impairment [111, 112], and there can be a high susceptibility to adverse events when hypertension and diabetes are treated intensively [85, 103, 104]. The evidence of benefit from pharmacotherapies in PAD has been mostly extrapolated from lower risk cohorts [29]. There is no consensus regarding the role of intensive medical therapy, and more research is needed to guide clinical practice.

1.4.2. Weight loss in obesity

Weight loss for people with obesity is recommended for the general population. Many potential benefits relate to a reduction in blood pressure, hypertriglyceridaemia, hyperglycaemia, inflammation and obstructive sleep apnoea [113]. Whether such benefits translate to improved long-term cardiovascular outcomes in PAD is unclear. A meta-analysis combined seven observational studies of PAD and showed that obesity was associated with a 9% increased risk of MACE [114]. Similar to coronary artery disease, an obesity paradox has been described in PAD [115]. A study of 2,392 patients that underwent major vascular surgery found an inverse relationship between the body mass index (BMI) and mortality. Obese (BMI >30) and overweight (BMI =25-30) patients had more favourable outcomes than normal (BMI =18.5-24.9) and underweight (BMI <18.5) people. However, there was an over-representation of chronic respiratory disease in normal and underweight people, where a low BMI can be detrimental [116]. PAD has an association with chronic respiratory disease, primarily due to high smoking use in these patient populations [117]. Therefore, medical comorbidities, such as chronic respiratory disorders, are relevant when considering a weight loss intervention. More research is needed to characterise the impact of a weight loss intervention on the risk of MACE and mortality.

1.4.3. Inflammatory control

Elevated inflammation, as quantified by high-sensitivity C-reactive protein (hs-CRP), correlates with an increased incidence of MACE and mortality [118, 119]. Some cardiovascular benefits of statins have been related to a reduction in hs-CRP [120]. CANTOS was a recent cardiovascular outcome study that investigated the efficacy of canakinumab, which directly acts in lowering inflammation. A total of 10,061 participants with previous myocardial infarction and elevated hs-CRP (> 2mg/L) were randomised to canakinumab or placebo. In the canakinumab-treated individuals that achieved a hs-CRP <2 mg/L, there was a 25% relative risk reduction in MACE, compared to on-treatment participants that had persistently elevated hs-CRP. These findings demonstrate the efficacy of lower inflammation in high-risk patients [121, 122]. However, canakinumab is not yet commercially available and has not been studied in PAD patients.

1.4.4. High-density lipoprotein cholesterol

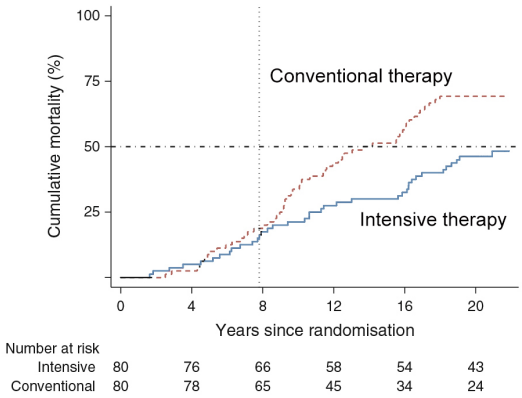
Low high-density lipoprotein cholesterol (HDL-C) is a widely accepted risk factor for cardiovascular disease [123] and has been associated with symptomatic PAD [15, 124, 125]. Where LDL-C lowering therapies have been shown to reduce MACE, medications targeting an increase in HDL-C have been ineffective [126]. One hypothesis is that these treatments do not address the qualitative abnormalities of HDL-C, which is common in coronary artery disease [127]. Dysfunctional HDL, as defined by a low HDL-mediated cholesterol efflux capacity (HDL CEC), is an independent predictor of MACE [128, 129]. The infusion of reconstituted HDL into patients has been shown to increase cholesterol efflux capacity [130], and the effect on MACE is being tested in a randomised controlled trial [131]. No link has been established between dysfunctional HDL and atherogenesis in the peripheral arteries.

1.4.5. Multiple risk factor control

The evidence for prescribing preventative medications and achieving individual risk factor control in PAD has been discussed. However, the effect of intensive multiple risk factor control is not well understood. In the Steno-2 study, 160 people with type 2 diabetes and microalbuminuria were randomised to receive either a multifactorial intervention or standard care for 7.8 years. These participants were subsequently followed for 13.4 years after this intervention (21.2 years following randomisation) [132, 133]. The risk factor targets that were set were a glycosylated haemoglobin <6.5%, fasting total cholesterol <4.5 mmol/L (175 mg/dL), fasting triglyceride level <1.7 mmol/L (150 mg/dL), systolic blood pressure <130 mmHg, and diastolic blood pressure <80 mmHg. The multifactorial intervention included: dietary modification with an emphasis on limiting saturated fat intake; light-to-moderate exercise for at least 30 minutes three to five times weekly; smoking cessation counselling for participants and their partners; daily vitamin and mineral supplementation; and a stepwise escalation in the pharmacological treatment of hyperglycaemia, hypertension, and dyslipidaemia. Angiotensin-converting enzyme (ACE) inhibitor or an angiotensin 2-receptor blocker were routinely prescribed [134]. Patients that were randomised to intensive treatment were more likely to achieve control of individual risk factors than those that were not, although these differences mostly attenuated after the intervention had ended [134]. At 21.2 years after randomisation, the multifactorial intervention was associated with a lower risk of mortality (HR 0.54, 95% CI, 0.32 to 0.89), major adverse cardiovascular or limb events (HR 0.41, 95% CI, 0.25 to 0.67), and the end-stage progression of diabetic nephropathy and retinopathy [132]. There was a delayed impact of intensive treatment on all-cause mortality (Figure 1.2). The divergence in outcomes, according to treatment groups, was more pronounced in the years after the intervention, indicating a legacy effect (Figure 1.3) [132, 133].

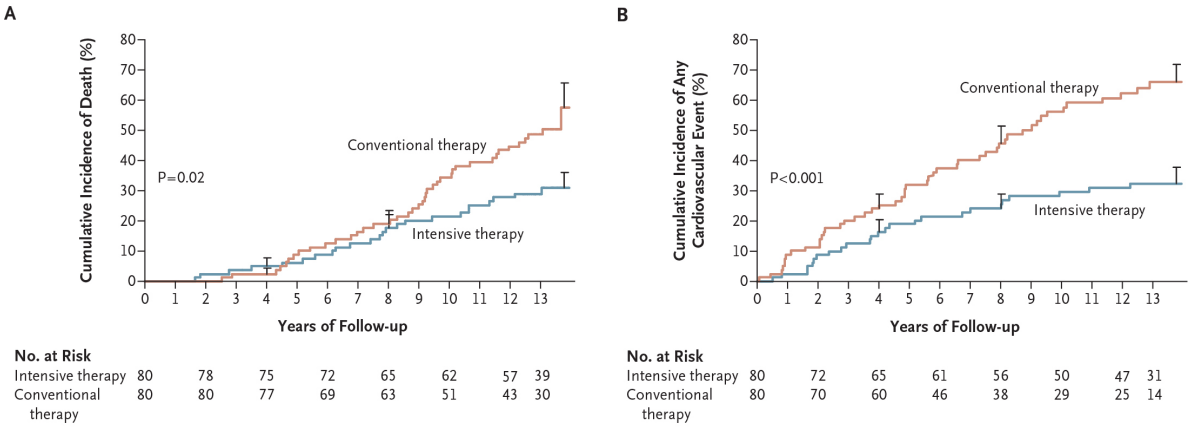
The Steno-2 study highlighted the benefits of addressing cardiovascular risk through the implementation of multiple strategies. However, there are limitations in extending these observations to PAD management today. The Steno-2 study began in 1993 when now proven treatments, such as ACE inhibitors and statins, may not have been as commonly prescribed. Since that time, risk factor control has evolved, with lower blood pressure and LDL-C targets, and new possibilities for lowering hs-CRP and triglycerides [135]. Given the walking constraints ascribed to intermittent claudication, a lifestyle intervention for PAD should differ from uncomplicated diabetes. The clinical phenotype of PAD, as it relates to functional status, concomitant risk factors and medical comorbidities, can vary from other high-risk conditions [1, 17, 136-139]. REACH was a prospective international study that followed 8,322 people with PAD for up to four years, among other high-risk individuals. A post hoc analysis of PAD patients found multiple risk factor control to be associated with a reduction in 1-year MACE. Like with the Steno-2 study, this analysis was in an era where risk factor control was less stringent [10]. Therefore, the risks and benefits of implementing a multifactorial intervention for PAD in a contemporary setting need further clarification.

Figure 1.2: Kaplan-Meier survival curve from randomisation, according to Steno-2 treatment group



Reproduced from Gaede P, Oellgaard J, Carstensen B, *et al.* Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial. Diabetologia. 2016;59(11):2298-307. Published online 2016 Aug 16. DOI: 10.1007/s00125-016-4065-6. Copyright © Gaede *et al.* 2016. Open access article under the terms of the Creative Commons Attribution License. [133]. Adapted with the addition of colour.

Figure 1.3: Kaplan-Meier event curves after intervention, according to Steno-2 treatment group



Panel A shows the cumulative incidence of all-cause mortality during the 13.3-year study period. Panel B shows the cumulative incidence of major adverse cardiovascular or limb event (composite of cardiovascular-related mortality, non-fatal stroke, non-fatal myocardial infarction, coronary artery bypass graft operation, percutaneous coronary intervention, peripheral artery revascularisation, lower extremity amputation).

Reproduced with permission from Gaede *et al.* Effect of a multifactorial intervention on mortality in type 2 diabetes, N Engl J Med 2008 Feb 7;358(6):580-91. DOI: 10.1056/NEJMoa0706245. Copyright © Massachusetts Medical Society 2008 [132].

1.4.6. Gender differences

There are many issues in PAD that weigh against women. Females are more likely to be asymptomatic or have atypical symptoms, further challenging clinical diagnosis [140, 141]. In observational studies, women with PAD had a more significant walking impairment and functional decline than their male counterparts [141, 142]. The efficacy of medical and lifestyle treatments is less well established in females, as they were commonly under-represented in clinical studies [140]. With potential differences in diagnosis, clinical manifestations and treatment, a divergence in long-term outcomes might occur. Gender differences in long-term MACE and mortality need further investigation, as this can provide further insights into PAD management.

1.4.7. Diagnosis and screening

The early stages of PAD are frequently asymptomatic and under-diagnosed [8, 9]. An ankle-brachial index (ABI) is a simple bedside test that has high sensitivity and specificity for PAD [19]. Population studies have demonstrated that an abnormal ABI corresponds with the risk of mortality, independent of Framingham-based risk score [20]. The national guidelines recommend a risk-stratified approach to manage cardiovascular risk factors, but they do not endorse screening for asymptomatic PAD [143, 144]. A compelling indication for PAD screening would be in populations where it is highly prevalent, while the estimation of cardiovascular risk is difficult. There are striking health disparities that affect Indigenous people, including premature atherosclerotic cardiovascular disease [145]. The utility of screening for PAD to improve cardiovascular risk-stratification in Indigenous Australians is not well understood.

1.5. Aims of the research study

The aims of this research concerning PAD are:

1. To identify factors that drive MACE and mortality and how this differs from coronary artery disease.
2. To identify associations with novel cardiovascular risk factors.
3. To evaluate gender differences in long-term outcomes.
4. To identify factors associated with major adverse limb events.
5. To evaluate the use of risk algorithms for managing patients.
6. To identify strategies for improving cardiovascular and mortality outcomes.

1.6. Hypotheses

The hypotheses regarding PAD are:

1. There are differences in clinical complexity compared to coronary artery disease patients that drive MACE and mortality.
2. Dysfunctional high-density lipoprotein cholesterol contributes to the pathogenesis.
3. Clinical factors that weigh against PAD-affected women translate into a higher likelihood of MACE and mortality.
4. There are differences in lower limb and mortality outcomes depending on the type of lower extremity revascularisation performed.
5. Screening for early disease can improve cardiovascular risk-stratification.
6. Risk algorithms can improve management decisions.
7. Intensive multiple risk factor is an effective strategy for improving long-term outcomes.

CHAPTER 2: CARDIOVASCULAR RISK FACTOR CONTROL AND OUTCOMES IN PAD – THE ACCELERATE TRIAL

ABSTRACT

Introduction: Prior studies have demonstrated adverse cardiovascular risk in patients with peripheral artery disease (PAD) and suboptimal control of risk factors. The impact of intensive risk factor control on outcomes in PAD patients has not been well characterised.

Methods: ACCELERATE was a randomised trial of evacetrapib and placebo in 12,092 statin-treated patients with atherosclerotic cardiovascular disease followed for a median of 28 months. Major adverse cardiovascular events (MACE) and all-cause mortality rates were compared in patients with PAD (n = 2,355) and coronary artery disease (CAD)-only (n = 9,274), in the setting of intensive risk factor control. The association between the individual or multiple risk factor control and MACE was evaluated in the PAD patients.

Results: In patients with PAD, there was a higher rate of MACE (17.0% vs 13.3%, p<0.001), cardiovascular mortality (5.3% vs 2.2%, p<0.001), non-fatal myocardial infarction (2.7% vs 1.5%, p=<0.001), non-fatal stroke (2.7% vs 1.5%, p=0.002) and all-cause mortality (8.2% vs 3.6%, p<0.001), when compared with CAD-only. An increase in MACE for PAD was observed even in the setting of an HbA1c <7.0% (12.8% vs 10.7%, p=0.02), LDL-C <70mg/dL (15.7% vs 11.4%, p<0.001), systolic BP <130 mmHg (13.8% vs 11.0%, p=0.01), diastolic BP <80 mmHg (15.9% vs 12.0%, p<0.001), triglycerides <150 mg/dL (14.1% vs 11.9%, p=0.02), non-smoking (15.6% vs 12.3%, p<0.001), and multiple risk factor control (14.0% vs 11.1%, p=0.004), in comparison with CAD-only. For PAD patients that achieved optimal glycaemia, LDL-C, systolic BP, diastolic BP, triglycerides, BMI, and smoking abstinence, individually or in combination, there was no associated relative risk reduction in MACE. Optimal hs-CRP levels were the lone risk factor that correlated with improved cardiovascular outcomes (HR 0.78, 95% CI, 0.61 to 0.99, p=0.05).

Conclusions: Despite intensive risk factor modification, elevated MACE rates continued to be observed in PAD, suggesting the need to develop new approaches to reducing cardiovascular risk in these patients.

2.1. Introduction

Peripheral artery disease (PAD) is estimated to affect 5 to 10% of people in Western countries, and this number increases to 20% of the population above 70 years of age [6]. The diagnosis of PAD is associated with a high risk of major adverse cardiovascular events (MACE) [93]. The American Heart Association (AHA) and the European Society of Cardiology recommend several medical and lifestyle therapies for all PAD patients to improve cardiovascular outcomes [19, 61]. The introductory chapter reviewed the evidence for these guidelines. PAD patients were studied in randomised controlled trials of antiplatelets, anticoagulants, statins, angiotensin-converting enzyme inhibitors (ACEI), angiotensin-2 receptor blockers (ARB), and protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors [52, 53, 59, 63, 69, 70, 86, 146]. However, the role of intensive multiple risk factor control of hypertension, dyslipidaemia, diabetes, and inflammation is still unclear. Previous diabetes studies have shown that multiple risk factor control can improve cardiovascular outcomes, in a way, where the sum of the parts does not equal the whole [132, 134]. The REACH registry was a prospective international study that followed 8,322 people with PAD for up to four years, among other high-risk individuals. For these PAD participants, multiple risk factor control was associated with a relative risk reduction in 1-year MACE. However, this cohort was followed over a decade ago, and only 5% of PAD patients achieved optimal control of all cardiovascular risk factors [10]. Today, there is more evidence for intensive blood pressure and lipid-lowering for cardiovascular disease, below the targets that were standard at that time [147]. High-sensitivity C-reactive protein (hs-CRP) could be a target for preventative therapies [135]. Therefore, the impact of contemporary multiple risk factor control on cardiovascular outcomes in PAD has not been well characterised.

ACCELERATE (Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at High Risk for Vascular Outcomes) was a phase 3

clinical study, which investigated the effects of evacetrapib therapy on MACE. In this analysis of the ACCELERATE trial, MACE rates were compared between patients with PAD and coronary artery disease (CAD)-only, in the setting of intensive risk factor control. Furthermore, we examined whether risk factor control correlated with more favourable cardiovascular outcomes in PAD.

2.2. Methods

2.2.1. Trial design

ACCELERATE was a multicentre, randomised, double-blind, placebo-controlled trial, which compared the effects of evacetrapib and placebo in 12,092 statin-treated patients with atherosclerotic cardiovascular disease. Details of the study design, objectives, methods, and endpoints have previously been published [148]. The trial was sponsored by Eli Lilly and was coordinated by the Cleveland Clinic Coordinating Center for Clinical Research (C5Research) and Covance (Princeton, NJ).

2.2.2. Trial population

For inclusion, participants had at least one of the following conditions: an acute coronary syndrome within the previous 30 to 365 days, atherosclerotic cerebrovascular disease, PAD, or diabetes with coronary artery disease. The criteria for inclusion as PAD was defined as current intermittent claudication or resting limb ischaemia and either an ankle-brachial index ≤0.90 or history of atherosclerotic limb ischaemia leading to previous non-coronary revascularisation or amputation. Some people with a PAD history were included based on other study eligibility criteria. Participants were required to receive the maximally tolerated dose for at least 30 days before screening. Statin-use was required for participation unless there was a history of side

effects or contraindications. Participants were required to have a high-density lipoprotein cholesterol (HDL-C) level of less than 80 mg/dL (2.10 mmol/L) and a triglyceride level of less than 400 mg/dL (4.52 mmol/L). The low-density lipoprotein cholesterol (LDL-C) levels at enrolment were to be no more than 10 mg/dL (0.25 mmol/L) or above target levels that were specified at the investigator's discretion.

2.2.3. Study aims

The primary endpoint of ACCELERATE was the first occurrence of a MACE, as a composite of cardiovascular-related mortality, non-fatal myocardial infarction, non-fatal stroke, coronary revascularisation, or hospitalisation for unstable angina. There was no significant difference in the primary outcome between patients receiving evacetrapib and placebo, and the study was terminated after a mean duration of follow-up of 28 months.

The aims of this analysis of ACCELERATE were to (1) compare the incidence of MACE and mortality in PAD and coronary artery disease (CAD)-only patients, (2) evaluate MACE in the setting of intensive individual and combined risk factor control, and (3) use logistic regression to test for associations between risk factor control and MACE in PAD.

2.2.4. Stratification of optimal risk factor control

Risk factors were evaluated at baseline and throughout the study. Each risk factor was categorised as "controlled" if the target was achieved at the three-month review. This analysis focused on the following seven risk factor targets: glycated haemoglobin (HbA1c) <7.0%, systolic blood pressure <130 mmHg, diastolic blood pressure <80 mmHg, LDL-C <70 mg/dL (1.80 mmol/L), triglycerides <150 mg/dL (1.70 mmol/L), high-sensitivity C-reactive protein

(hs-CRP) <2.0 mg/L, and smoking abstinence [19, 61, 135]. Smoking abstinence was defined as cessation from smoking for at least three months preceding assessment. Where ≥4 of 7 targets were realised, patients were classified as having "more optimal" control; whereas <4 of 7 targets met was consider "less optimal" control. A body mass index (BMI) <25 was an additional target in further analysis of PAD patients.

2.2.5. Statistical analysis

Clinical characteristics of participants were compared using the Wilcoxon test for continuous variables and chi-square test for categorical variables. Kaplan-Meier survival curves were created for the rate of the first occurrence of MACE. Comparisons were made between the incidence of MACE in PAD patients that achieved individual or multiple risk factor control, with those that did not. The adjusted analysis corrected for group differences in other significant variables identified with Cox regression. The associations were reported as hazard ratios (HR) with a 95% confidence interval, where $p<0.05$ was considered significant. All analyses used STATA 15.1 (StataCorp, College Station, TX).

2.3. Results

2.3.1. Patient characteristics

Of 12,092 total patients, 2,355 (19.5%) had PAD, including 752 (6.2%) PAD-only and 1,603 (13.3%) with concomitant PAD and CAD. There were 9,234 (76.4%) patients with CAD-only. The median overall duration of follow-up was 28 months (interquartile range, 26 to 30 months). The baseline demographics, disease-specific diagnoses, and medication-use are summarised in Table 2.1. Patients with PAD were older (mean age, 66.5 vs 63.9, $p<0.001$), more frequently female (26.6% vs 21.5%, $p<0.001$), less likely to have diabetes (58.3% vs 72.1%, $p<0.001$),

and higher current smoking (25.8% vs 13.8%, p<0.001) and cerebrovascular disease (36.4% vs 15.7%, p<0.001), compared with CAD-only. In PAD patients with concomitant CAD, there was lesser history of acute coronary syndrome (36.6% vs 69.6%, p<0.001) and percutaneous coronary intervention (62.0% vs 73.0%, p<0.001). PAD patients had higher use of anti-hypertensive agents (89.5% vs 86.8%, p<0.001) but were less likely to be treated with aspirin (74.2% vs 85.7%, p<0.001), statins (95.5% vs 96.6%, p=0.01), and ACEI or ARB (76.0% vs 78.6, p<0.001), compared to those without.

Table 2.1: Baseline characteristics

Characteristic	PAD (N = 2,355)	CAD-only (N = 9,274)	p value
Age (mean years)	66.5 ± 8.8	63.9 ± 9.5	<0.001
Males (%)	73.4	78.5	<0.001
White (%)	87.7	80.5	<0.001
BMI (mean)	29.6±5.4	30.4±5.8	<0.001
Current smoking (%)	25.8	13.8	<0.001
Diabetes (%)	58.3	72.1	<0.001
Cerebrovascular disease (%)	36.4	15.7	<0.001
Coronary artery disease (%)	68.1	100.0	<0.001
Prior acute coronary syndrome	36.6	69.6	<0.001
Prior percutaneous coronary intervention	62.0	73.0	<0.001
Prior CABG	43.5	26.8	<0.001
Peripheral artery disease (%)	100.0	0.0	
PAD criteria inclusion	71.1	-	
Ankle brachial index ≤0.9	84.6	-	
Non-coronary revascularisation in response to ischaemia	44.4	-	
Prior amputation	4.9	-	
Baseline medication use (%)			
Statin	95.5	96.6	0.01
ACE inhibitor or ARB	76.0	78.6	<0.001
Aspirin	74.2	85.7	<0.001
Beta blocker	65.6	78.8	<0.001
Calcium channel blocker	34.3	26.7	<0.001
Diabetic medication	53.0	63.3	<0.001
Anti-hypertensive medication	89.5	86.8	<0.001

Age and BMI expressed as mean±standard deviation. ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin 2 receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft

2.3.2. Risk factor control

Table 2.2 summarises the risk factor control of participants with PAD and CAD-only. The patients with PAD were more likely to achieve a HbA1c <7.0% (61.2% vs 53.8%, p<0.001), but less likely to achieve a LDL-C <70 mg/dL (55.4% vs 58.0, p=0.03), systolic BP <130 mmHg (39.6% vs 50.3%, p=0.001), smoking abstinence (74.2% vs 86.2%, p<0.001) and hs-CRP <2 mg/L (49.2% vs 60.4%, p<0.001), compared to those with CAD-only. A lower percentage of patients with PAD were classified as achieving more optimal control compared to those without (68.0% vs 72.9%, p<0.001).

Table 2.2: Percentage of people achieving risk factor control at 3-month follow-up

Risk Factor (% of people)	PAD (N = 2,355)	CAD-only (N = 9,274)	p value
HbA1c <7%	61.2	53.8	<0.001
LDL-C <70 mg/dL	55.4	58.0	0.03
Triglycerides <150 mg/dL	65.8	65.6	0.89
Systolic BP <130 mmHg	39.6	50.3	0.001
Diastolic BP <80 mmHg	66.9	65.0	0.09
Hs-CRP <2 mg/L	49.2	60.4	<0.001
Non-smoker	74.2	86.2	<0.001
Risk factor control			<0.001
Less optimal (<4 of 7)	32.0	27.1	
More optimal (≥4 of 7)	68.0	72.9	

BP, blood pressure; HbA1c, glycated haemoglobin; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol

2.3.3. Incidence of MACE and all-cause mortality

There was a higher rate of MACE (17.0% vs 13.3%, p<0.001), cardiovascular mortality (5.3% vs 2.2%, p<0.001), non-fatal myocardial infarction (2.7% vs 1.5%, p<0.001), non-fatal stroke (2.7% vs 1.5%, p=0.002) and all-cause mortality (8.2% vs 3.6%, p<0.001) in patients with PAD compared with CAD-only (see Table 2.3 and Figure 2.1). Greater MACE rates were observed in PAD patients even in the setting of HbA1c <7.0% (12.8% vs 10.7%, p=0.02), LDL-C <70mg/dL (15.7% vs 11.4%, p<0.001), systolic BP <130 mmHg (13.8% vs 11.0%, p=0.01), diastolic BP <80 mmHg (15.9% vs 12.0%, p<0.001), triglycerides <150 mg/dL (14.1% vs 11.9%, p=0.02), non-smoking (15.6% vs 12.3%, p<0.001), and hs-CRP <2 mg/L (13.2% vs 11.3%, p=0.10), compared to those without PAD (see Table 2.4 and Figure 2.2). Patients with PAD classified as having more optimal control had a higher incidence of MACE than the matched CAD-only group (14.0% vs 11.1%, p=0.004).

Table 2.3: Incidence of first occurrence MACE and all-cause mortality

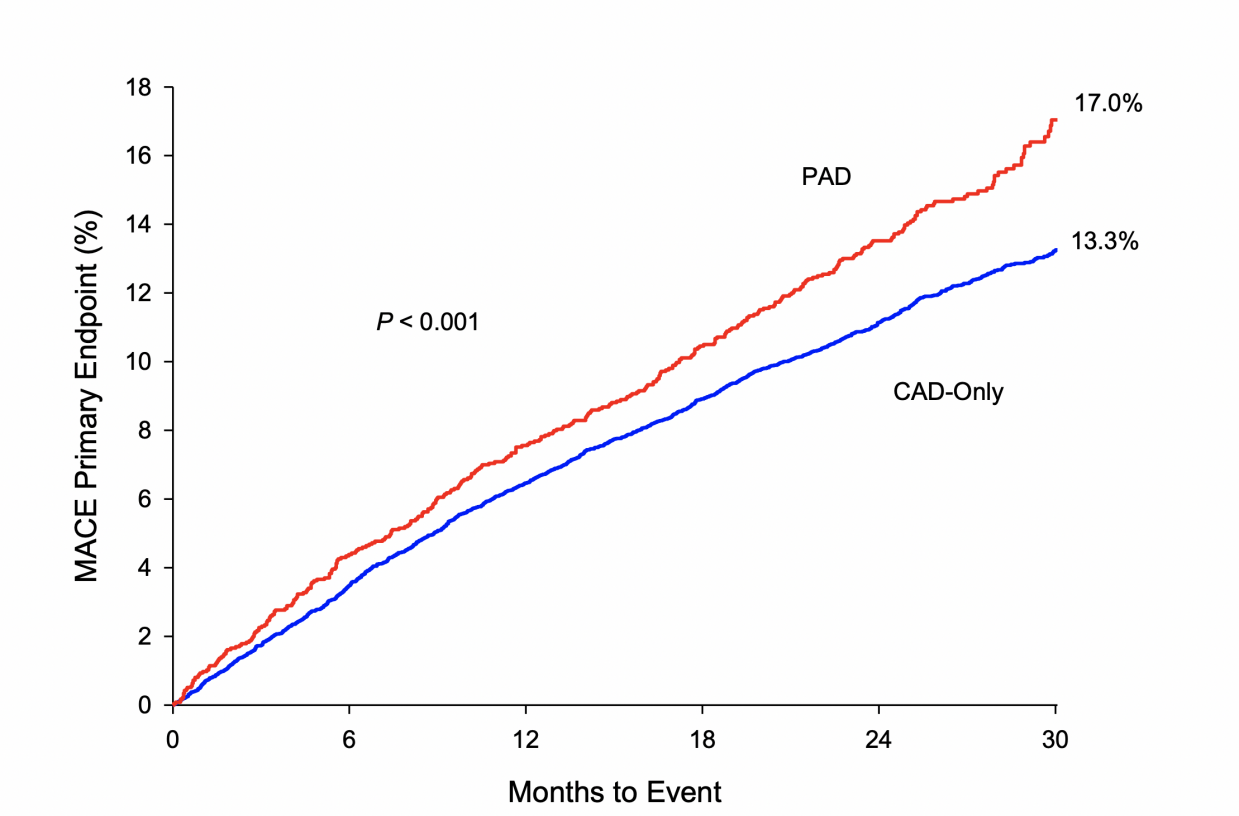
Event	PAD (N = 2,355)	CAD-only (N = 9,274)	p value
Major adverse cardiovascular events (%)	17.0	13.3	<0.001
Cardiovascular mortality	5.3	2.2	<0.001
Non-fatal myocardial infarction	6.2	4.3	<0.001
Non-fatal stroke	2.7	1.5	0.002
Hospitalisation for unstable angina	2.9	2.8	0.89
Coronary revascularisation	8.4	9.0	0.25
All-cause mortality (%)	8.2	3.6	<0.001

Table 2.4: Incidence of first occurrence of MACE, according to risk factor control

Risk factor control	PAD (N = 2,355)	CAD-only (N = 9,274)	p value
Diabetes (%)			
HbA1c <7.0%	12.8	10.7	0.02
HbA1c ≥7.0%	16.2	13.4	0.03
LDL-C (%)			
LDL-C <70 mg/dL	15.7	11.4	<0.001
LDL-C ≥70 mg/dL	13.3	13.0	0.75
Systolic BP (%)			
Systolic BP <130 mmHg	13.8	11.0	0.01
Systolic BP ≥130 mmHg	15.4	13.2	0.03
Diastolic BP (%)			
Diastolic BP <80 mmHg	15.9	12.0	<0.001
Diastolic BP ≥80 mmHg	12.5	12.3	0.86
Triglycerides (%)			
Triglycerides <150 mg/dL	14.1	11.9	0.02
Triglycerides ≥150 mg/dL	15.9	12.0	0.002
Hs-CRP (%)			
Hs-CRP <2 mg/L	13.2	11.3	0.10
Hs-CRP ≥2 mg/L	17.0	13.7	0.01
Smoking (%)			
Non-smoker	15.6	12.3	<0.001
Current smoker	13.5	13.0	0.79
Multiple risk factor control			
More optimal (4 to 7)	14.0	11.1	0.004
Less optimal (0 to 3)	15.8	14.2	0.31

BP, blood pressure; HbA1c, glycated haemoglobin; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol

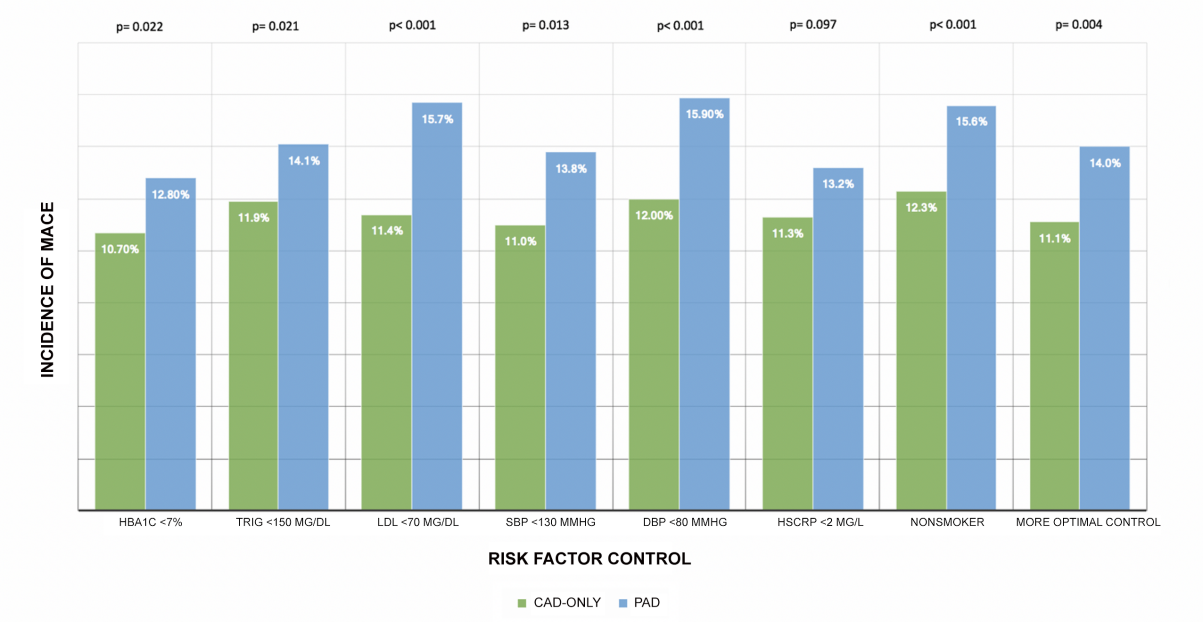
Figure 2.1: Kaplan-Meier survival curve for first occurrence of MACE in PAD and CAD-only patients



Number at risk

PAD	2,355	2,239	2,146	2,055	1,782	463
CAD-only	9,274	8,936	8,635	8,371	7,470	2,088

Figure 2.2: Incidence of MACE for PAD and CAD-only patients, in the setting of optimal risk factor control



DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; HSCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein cholesterol; RF, risk factor; SBP, systolic blood pressure; TRIG, triglycerides.

2.3.4. Associations between risk factor control and MACE in PAD

Logistic regression analysis was performed to assess the impact of individual or multiple risk factor control on MACE in the PAD patients (Table 2.5). Optimal control of glycaemia (adjusted [adj.] HR 0.96, 95% CI, 0.73 to 1.26, p=0.75), LDL-C (adj. HR 1.05, 95% CI, 0.84 to 1.32, p=0.67), systolic BP (adj. HR 0.90, 95% CI 0.72 to 1.13, p=0.36), diastolic BP (adj. HR 1.09, 95% CI 0.85 to 1.39, p=0.50), triglycerides (adj. HR 0.85, 0.66 to 1.13, p=0.16), BMI (adj. HR 0.91, 95% CI, 0.68 to 1.21, p=0.51), and smoking abstinence (adj. HR 1.00, 95% CI, 0.77 to 1.29, p=0.99), were not associated with reduced MACE. Multiple risk factor control, as defined in Table 2.5, did not significantly correlate with less MACE (adj. HR 1.13, 95% CI,

0.88 to 1.45, p=0.36). Hs-CRP was the lone risk factor target that was independently associated with improved cardiovascular outcomes (adj. HR 0.78, 95% CI, 0.61 to 0.99, p=0.05).

Table 2.5: Adjusted* hazard ratio for risk factor control and MACE in PAD

Risk factor control	MACE		
	HR	95% CI	p value
HbA1c <7.0% vs ≥7.0%	0.96	0.73 – 1.26	0.75
LDL-C <70 mg/dL vs ≥70 mg/dL	1.05	0.84 – 1.32	0.67
Systolic BP <130 mmHg vs ≥130 mmHg	0.90	0.72 – 1.13	0.36
Diastolic BP <80 mmHg vs ≥80 mmHg	1.09	0.85 – 1.39	0.50
Triglycerides <150 mg/dL vs ≥150 mg/dL	0.85	0.66 – 1.13	0.16
Hs-CRP <2 mg/L vs ≥2 mg/L	0.78	0.61 – 0.99	0.05
Smoking abstinence vs smoking	1.00	0.77 – 1.29	0.99
BMI ≤ 25 vs >25	0.91	0.68 – 1.21	0.51
4 to 8 vs 0 to 3 risk factors controlled †	1.13	0.88 – 1.45	0.36

** Adjusted for significant variables identified using Cox regression (age, amputation for PAD, non-coronary revascularisation in response to limb ischaemia, cerebrovascular disease, coronary artery disease, acute coronary syndrome, diabetes, and statin-use). † BMI ≤ 25 was an additional risk factor target added for Table 2.5. Abbreviations: BMI, body mass index; BP, blood pressure; HbA1c, glycated haemoglobin; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol*

2.4. Discussion

In this analysis of the ACCELERATE trial, higher rates of MACE were seen for PAD, even in the setting of smoking abstinence, or optimal glycaemic, lipid, blood pressure, and inflammatory control, compared to CAD-only. These PAD patients appeared relatively well-managed, compared to prior observational studies [10, 12]. Here, more intensive individual and multiple risk factor control were not independently associated with more favourable cardiovascular outcomes. These findings underscore the challenges with altering the clinical course of PAD and indicate a need for new strategies, including inflammatory control.

These findings differ from many prior observations of PAD patients, where an under-prescription of medical therapies has been previously described [10, 13, 149, 150]. One study audited the usage of guideline-recommended therapies for PAD patients in 1,982 US clinic visits between 2005 and 2012. There was strikingly low utilisation of antiplatelets (35.7% of visits), statins (33.1%), ACEI or ARB (28.4%), and counselling or medication for smoking cessation (35.8%) [12]. In that setting, high rates of MACE can be expected. A strength of analysing ACCELERATE was that the PAD patients were frequently prescribed statins (94%), ACEI or ARB (72%), and anti-hypertensives (90%), and were mostly non-smokers (74%). The benefits of smoking abstinence and these medical treatments are not in question [147]. However, intensively treating hypertension, dyslipidaemia, diabetes, obesity, elevated inflammation, alone and in combination, in PAD patients has not been well researched. The high MACE rates in ACCELERATE were not attributable to smoking or an under-prescription of proven therapies, as often occurs with studies in this space.

Prior diabetes studies have demonstrated the potential benefits of intensive multiple risk factor control. In the Steno-2 study, 160 people with type 2 diabetes and microalbuminuria were randomised to receive either a multifactorial intervention or standard care for 7.8 years.

These participants were subsequently followed for 13.4 years after this intervention (21.2 years following randomisation). The risk factor targets that were set were an HbA1c <6.5%, fasting total cholesterol <4.5 mmol/L (175 mg/dL), fasting triglyceride level <1.7 mmol/L (150 mg/dL), systolic BP <130 mmHg, and diastolic BP <80 mmHg. At 21.2 years after randomisation, the multifactorial intervention was associated with a lower risk of mortality (HR 0.54, 95% CI, 0.32 to 0.89), major adverse cardiovascular or limb events (HR 0.41, 95% CI, 0.25 to 0.67) [132-134]. The Steno-2 study highlighted the benefits of addressing cardiovascular risk through the implementation of several strategies. However, there are drawbacks to extending these observations to PAD management today. The study began in 1993 when now established treatments, including ACE inhibitors and statins, may not have been as commonly prescribed. Risk factor control has since evolved, with lower BP and LDL-C targets, and new possibilities for lowering hs-CRP and triglycerides [84, 93, 122, 151]. There is walking impairment ascribed to intermittent claudication, which means a lifestyle intervention for PAD is distinct from uncomplicated diabetes. The clinical phenotype of PAD, as it relates to functional status, concomitant risk factors and medical comorbidities, can significantly vary from other high-risk conditions [1, 17, 136-139]. Therefore, the risks and benefits of intensively treating these patients differ, and this may, at least partly, explain the disappointingly low prescription of proven therapies that have been observed.

There are other possible explanations for the high incidence of MACE in PAD, compared to CAD-only. The presence of concomitant PAD and CAD indicates a propensity for aggressive atherosclerotic disease. In a prior study, serial intravascular ultrasound imaging was used to compare coronary artery plaque burden and progression in 3,479 patients with and without PAD. The patients with concomitant PAD had more extensive and calcified coronary atherosclerosis and disease progression during serial follow-up [152]. High atherosclerotic

plaque burden on coronary intravascular ultrasound has been correlated with elevated rates of MACE [153].

The PAD cohort in ACCELERATE might have been negatively impacted by physical inactivity, given they are hallmarks of intermittent claudication; although this was not assessed [18]. A prior study of 15,486 patients with stable CAD found that moderate or high-intensity physical activity was associated with lower mortality (including cardiovascular-related mortality), compared with physical inactivity. The relationship between sedentary lifestyle and mortality was stronger in people classified as high-risk, which included PAD [154]. Another study assessed activity levels of 1,288 participants that underwent an elective coronary angiography. The individuals who self-reported regular and vigorous activity were less likely to have concomitant PAD, and this was associated with lower mortality during follow-up [41].

Inflammatory control could be a new strategy for improving cardiovascular outcomes in PAD. Lipid-lowering therapies have been shown to have pleiotropic benefits relating to hs-CRP reduction [120, 155]. More recently, CANTOS was a clinical trial that tested the efficacy of a monoclonal antibody targeting interleukin-1β. A total of 10,061 participants with previous myocardial infarction and elevated hs-CRP (> 2mg/L) were randomised to placebo or canakinumab (50 mg, 150 mg or 300 mg) three-monthly subcutaneous injection. Canakinumab-treated individuals who achieved a hs-CRP <2 mg/L after an initial dose, had a 25% relative risk reduction in MACE, compared to on-treatment participants with persistently elevated hs-CRP (≥ 2mg/L). These findings demonstrated how directly targeting elevated inflammation can improve cardiovascular outcomes [122].

While anti-inflammatory medications appear promising, their incorporation into clinical practice will require consideration for long-term safety and cost-effectiveness. Lifestyle modification, including exercise and weight loss in obesity, is often emphasised in

PAD [147], and this can theoretically reduce inflammation [156-158]. The AHA recommends supervised exercise training in symptomatic PAD, consisting of 30 to 45-minute sessions, performed at least three times per week for at least twelve weeks [19]. Studies that have associated exercise with a lesser risk of MACE and mortality were observational. There are difficulties with powering a clinical study to test the impact of lifestyle modification on cardiovascular outcomes. One alternative is to evaluate inflammatory marker reduction as a surrogate endpoint. Some PAD research has examined the effect of supervised exercise therapy on hs-CRP, although results have been inconsistent [156, 159]. These studies were limited by size, and duration of treatment or follow-up, and they did not target individuals with suboptimal inflammatory control. More research is needed into long-term training strategies that might lead to continued reduction in the markers of inflammation.

In ACCELERATE, a BMI<25 was not associated with less MACE in PAD. Obesity has been previously associated with increased MACE [160]. Despite this link, weight loss in obesity might not always be advisable [115]. Weight loss in overweight and obese people is recommended for the general population and is associated with improved blood pressure, lipid, and glycaemic control [161]. However, PAD patients may have a higher degree of medical complexity, and an obesity paradox has been described, whereby a low or normal BMI is detrimental [162]. Other comorbidities, where elevated BMI is protective, such as chronic respiratory conditions, need to be considered.

The risk factor targets in this analysis were not specific to PAD. Most substantial evidence for intensive blood pressure lowering in secondary prevention extends from SPRINT. However, many groups, such as diabetes, cerebrovascular disease, and age greater than 75 years of age, were not examined in that trial [84]. Intensive glycaemic control in patients with established atherosclerotic cardiovascular disease was not shown to improve cardiovascular outcomes in randomised clinical trials [147, 163]. A post hoc analysis of diabetics in the

EUCLID trial did find that every 1% increase in HbA1c, was associated with a 14.2% increased relative risk for MACE [100]. While LDL-C <70 mg/dL is a conventional target, with the advent of new lipid-lowering therapies, more intensive LDL-C treatment could become the norm. PCSK9 inhibitors are associated with a reduction of MACE in PAD, and this correlation is evident even with very low LDL-C levels (< 10 mg/dL) [93]. High-dose omega-3 fatty acid supplementation reduced incidence of MACE in high-risk patients, including PAD, with a baseline triglyceride level of 135-499 mg/dL (1.52-5.63 mmol/L) and LDL-C of 41-100 mg/dl (1.06-2.59 mmol/L) [151]. Most participants in ACCELERATE were taking antiplatelet monotherapy, but this standard of care is also being challenged. In the PAD subset of COMPASS, combined rivaroxaban and aspirin was associated with a 31% relative risk reduction in MACE, compared with aspirin-alone [63]. The landscape of preventative therapy is changing, and new strategies need to be incorporated into PAD management.

Some caveats should be noted. ACCELERATE was a clinical trial with a specified inclusion and exclusion criteria. Differences in patient complexity need to be considered when extrapolating these findings to other clinical settings. In many prior PAD studies, proven therapies, including statins, antiplatelets, ACEI or ARB, were less frequently used [10, 89]. ACCELERATE allowed for the evaluation of intensive multiple risk factor control when these guideline-recommended medications were commonly prescribed. This analysis reported MACE and mortality outcomes according to risk factor control, but the potential unmeasured benefit of reducing major adverse limb events would be an additional impetus for treating PAD patients. Major adverse limb events are a cause of permanent disability, and this can be modified by medical therapies [31]. Approximately half of the PAD participants had a history of non-coronary revascularisation or lower extremity amputation, which indicates they were at high risk of future major adverse limb events [28]. ACCELERATE was a phase 3 trial designed to investigate the effects of evacetrapib, which is a cholesteryl ester transfer protein inhibitor.

In this analysis, 3-month risk factor control was used, as that was the time that the LDL-C-lowering effect of evacetrapib treatment plateaued. A decreased LDL-C level from evacetrapib did not correlate with a reduction in MACE [148], which is at odds with larger epidemiological studies [88]. Therefore, the relationship between lipid control (and other risk factors) and cardiovascular events could have been influenced by confounding. There was potential for significant heterogeneity in the duration of risk factor control, such as blood pressure. It can be expected that some participants achieved optimal control of hypertension for longer than others, dating before the commencement of the study. Prior diabetes studies have demonstrated a legacy effect, whereby cardiovascular benefits of risk factor control are seen years after medical prevention [132, 134]. The median study follow-up was 28 months and may have been too short to appreciate these effects. Some risk factors were not evenly distributed among the participants. For instance, there was a high proportion of non-smokers. Therefore, the power of the study to assess the effect of individual risk factor control could have been limited by the sample size. Despite these potential limitations, there was sufficient data to detect significant discrepancies between PAD and CAD-only patients.

2.5. Conclusions

The presence of PAD in patients with or without CAD was associated with an elevated cardiovascular risk, despite intensive risk factor modification. This indicates a need for additional strategies to improve long-term outcomes in patients with PAD.

CHAPTER 3: RISK FACTOR CONTROL AND CORONARY ARTERY ATHEROMA BURDEN AND PROGRESSION IN PAD

ABSTRACT

Background: Concomitant PAD in people with coronary artery disease (CAD) correlates with higher rates of major adverse cardiovascular events, even in the setting of intensive risk factor modification. One explanation is that PAD patients have high-risk coronary artery plaque that is more critical, diffuse and prone to thrombotic occlusion, although this has not been definitively proven. Intravascular ultrasound (IVUS) can be used to assess coronary artery atherosclerotic burden and progression, as it relates to risk factor control.

Methods: This post hoc analysis compared a PAD (n =48) and a non-PAD (n =240) cohort that was matched for age and gender. Data were derived from three clinical trials where coronary artery disease of moderate severity was monitored with serial IVUS. Images of matched arterial segments were taken at baseline and the end of the clinical trials and compared. Measurements performed included vessel size (lumen and external elastic membrane [EEM] volumes, mm^3), calcium (percent of images), and atherosclerotic plaque (percent atheroma volume [PAV, %] and total atheroma volume [TAV, mm^3]), with values expressed as mean ± standard deviation. The annualised change in atheroma was quantified while adjusting for baseline plaque features. Baseline plaque burden and disease progression were compared between PAD and non-PAD patients, according to risk factor control. The plaque progression in PAD patients that achieved individual and combined risk factor control was compared with those that did not.

Results: At baseline, PAD patients had a smaller EEM volume (253.5 ± 72.1 mm^3 vs 307.4 ± 103.7 mm^3, p=0.001), lumen volume (408.1 ± 111.6 mm^3 vs 486.9 ± 159.7 mm^3, p=0.001), lower TAV (154.6 ± 62.2 mm^3 vs 179.6 ± 74.1 mm^3, p=0.03), but comparable PAV (37.5 ± 8.2% vs 36.5 ± 8.7%, p=0.45) and calcium (33.1 ± 22.8% vs 26.7 ± 21.9%, p=0.06). There was no significant difference in the annualised change in PAV (-0.08 ± 0.31% vs -0.29 ± 0.24%,

p=0.40), and TAV (-1.83 ± 1.78 mm^3 vs -3.50 ± 1.37 mm^3, p=0.24), or the number of PAV progressors (14.6% vs 19.6%, p=0.42) and regressors (25.0% vs 35.4%, p=0.16) for PAD and non-PAD patients, respectively. The non-PAD group had a significant regression in the mean annualised TAV (mean change -3.50 mm^3, 95% CI, -6.19 and -0.80, p=0.01), but the PAD patients did not (mean change -1.83 mm^3, 95% CI, -5.33 to 1.66, p=0.30). More optimal risk factor control (mean difference -3.89, 95% CI, -7.35 to -0.42, p=0.03) and optimal triglycerides (mean difference -3.69, 95% CI, -7.04 to -0.34, p=0.03) was associated with more TAV regression in non-PAD than PAD patients, accordingly. In PAD patients achieving individual or combined risk factor control, there was no significant difference in PAV or TAV change, compared with PAD individuals that did not.

Conclusions: Contrary to previous research, people with concomitant PAD did not have higher coronary artery atherosclerotic burden or progression. Also, there was no observed effect of individual and multiple risk factor control on plaque progression, suggesting resilience to medical treatments. These findings are consistent with chapter two, where multiple risk factor control was not associated with a significant reduction in major adverse cardiovascular events in PAD. Further studies with serial IVUS can help establish the role of other management strategies.

3.1. Introduction

Peripheral artery disease (PAD) has been associated with a higher incidence of major adverse cardiovascular events (MACE), compared to other manifestations of atherosclerosis [53, 93]. In prior observational studies, PAD patients were not usually prescribed proven medical therapies, and risk factor control was largely inadequate [10, 12]. Therefore, an under-prescription of guideline-recommended treatments might, at least partly, explain the elevated rates of MACE that have been described [10, 11, 150]. In chapter 2, we examined a relatively well-managed PAD cohort, and still observed higher rates of MACE, compared with coronary artery disease-only. There was no evidence that multiple risk factor control was associated with more favourable cardiovascular outcomes. Here the mechanistic basis for these findings is explored.

A popular hypothesis is that PAD patients have high-risk coronary artery plaque properties that are more critical, diffuse and prone to thrombotic occlusion [164, 165]. Most studies that have attempted to prove this theory have been limited, as they were cross-sectional, used simple imaging modalities or were performed in an era before the widespread use of statins and other therapies [166-168]. The introductory chapter outlined the evidence for medical therapies in PAD, as they relate to hypertension, dyslipidaemia, hyperglycaemia and smoking. It is known from diabetes studies that control of multiple risk factors can have a more complex interaction, whereby the sum of the parts does not equal the whole [134, 169]. Although multiple risk factor control is recommended [147], little is known regarding the effect on the natural history of coronary artery atherosclerosis in PAD.

Intravascular ultrasound imaging (IVUS) can be used to calculate the atherosclerotic plaque burden. Many clinical trials have incorporated serial IVUS imaging to assess the impact of medical therapies on coronary artery atheroma over time [170]. There is a correlation

between atheroma burden and progression evaluated with IVUS and the incidence of subsequent MACE [153]. IVUS imaging can provide insight into the cardiovascular issues affecting people with PAD. One prior study that utilised serial IVUS imaging showed that concomitant PAD was associated with more extensive coronary atherosclerosis and accelerated disease progression [152]. However, the comparisons made with non-PAD patients did not account for demographic differences or risk factor control. To our knowledge, there have been no previous studies that have assessed how risk factor control (blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, high-sensitivity C-reactive protein, and smoking) alone and in combination can be associated with coronary atheroma progression in PAD. This analysis utilised a pool of results from clinical trials, where the participants underwent serial IVUS imaging. We examine how atherosclerotic burden and progression in the coronary circulation might differ, in the setting of multiple risk factor control, between patients with concomitant PAD and in those without.

3.2. Methods

3.2.1. Study population

This post hoc analysis examined PAD (n = 48) and non-PAD (n = 240) participants from three clinical trials. The non-PAD group was age and gender-matched with the PAD group. Serial IVUS imaging was used to investigate the impact of lipid-lowering medications on coronary atherosclerosis in all studies. Details of study design, objectives, methods, and primary endpoints have been published previously [171-173]. The three included trials were GLAGOV (global assessment of plaque regression with a PCSK9 antibody as measured by intravascular ultrasound trial) [173], SATURN (the study of coronary atheroma by intravascular ultrasound: effect of rosuvastatin vs atorvastatin) [171], and ASTEROID (a study to evaluate the effect of

rosuvastatin on intravascular ultrasound-derived coronary atheroma burden) [172]. In GLAGOV, PAD was an inclusion criterion defined as either: current intermittent claudication of presumed atherosclerotic origin with an ankle-brachial index ≤0.9; or history of intermittent claudication with prior lower extremity revascularisation or related amputation within the last two years. The SATURN and ASTEROID trials identified PAD patients based on a documented history. Broadly, participants were eligible if they had bystander coronary artery disease with luminal stenosis >20% in at least one major coronary artery, which was confirmed by angiography in a clinically indicated setting. All trials complied with the Declaration of Helsinki and were approved by institutional boards at participating sites.

3.2.2. Study aims

The aims of this analysis were to (1) compare baseline and serial measurements of coronary artery atherosclerotic plaque in PAD and non-PAD patients, (2) compare plaque progression in PAD and non-PAD patients, according to individual and combined risk factor control, (3) compare plaque progression in PAD patients that achieved risk factor control with those that did not.

3.2.3. IVUS imaging

Comprehensive details of the methods for IVUS imaging acquisition and analysis have been published [171-173]. In brief, images were acquired from an arterial segment of at least 30 mm in length and with luminal stenosis of 20 to 50%. This coronary artery was required to be a non-culprit vessel and not require treatment with coronary angioplasty. A high-frequency ultrasound transducer (30-40 MHz) was inserted distal to the stenosis. An automated pullback of the catheter was performed at a constant rate of 0.5 mm/s, while continuous ultrasound

images were obtained. IVUS was performed of the same arterial segment at baseline and study end. The follow-up duration varied between 20 and 26 months across the three studies.

IVUS images were digitised, and measurements were performed within a matched arterial segment (Figure 3.1). Cross-sectional images spaced precisely 1 mm apart were selected for analysis. The leading edges of the lumen (mm^3) and external elastic membrane (EEM, mm^3) were traced by manual planimetry. Areas between these leading edges were recognised as atherosclerotic plaque. Percent atheroma volume (PAV) was the proportion of the vessel wall that was occupied by plaque, as calculated using the following accepted equation [153]:

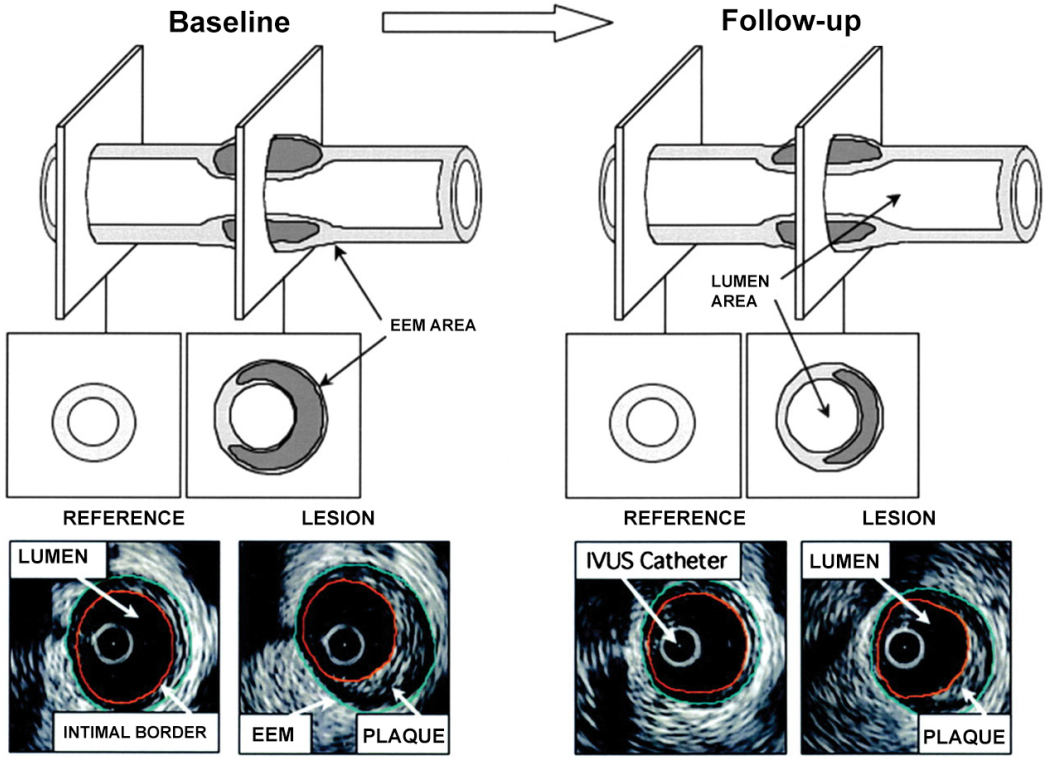
$$PAV\ (\%) = [\sum (EEM_{area} - LUMEN_{area}) / \sum EEM_{area}] \times 100$$

A normalised total atheroma volume (TAV), was the summation of plaque area in each measured image calculated the following equation:

$$TAV_{normalised}\ (mm^3) = [\sum (EEM_{area} - LUMEN_{area}) / \text{Number of slices in pullback}] \times \text{Median number of images in cohort}$$

These volumes were normalised to adjust for differences in segment length between subjects. Progression and regression were a >5% relative increase or decrease in PAV, respectively. The proportion of images where calcium was observed in at least one quadrant was quantified. All values were expressed as mean ± standard deviation.

Figure 3.1: Schematic for serial IVUS imaging measurements



This diagram shows a relatively normal area (reference) and the site of disease (lesion).

Hartmann M, Huisman J, Serial intravascular ultrasound assessment of changes in coronary atherosclerotic plaque dimensions and composition: an update, European Heart Journal – Cardiovascular Imaging. 2011 12(4):313-21 [170] Reproduced with permission from Oxford University Press, License number 4751150852242, License date Jan 17, 2020.

3.2.4. Stratification of risk factor control

The baseline and average follow-up risk factors were evaluated. A total of seven risk factors were quantified and the targets were as followed: systolic blood pressure (SBP) <130 mmHg, diastolic blood pressure (DBP) <80 mmHg, low-density lipoprotein cholesterol (LDL-C) <70 mg/dL (1.80 mmol/L), high-density lipoprotein cholesterol (HDL-C) >40 mg/dL (1.03 mmol/L), triglycerides <150 mg/dL (1.70 mmol/L), high-sensitivity C-reactive protein (hs-CRP) <2.0 mg/L, and smoking abstinence. Individuals that achieved 4 to 7 targets were categorised as having "more optimal" control. Otherwise, people meeting 0 to 3 risk factors targets were classified as having "less optimal" control.

3.2.5. Statistical analysis

Results are presented as percentages for categorical variables and mean ± SD for continuous variables. Clinical and plaque characteristics were compared by the Student *t*-test or analysis of variance for continuous variables as appropriate. For categorical variables, the chi-square test or Fisher's exact test was used. Changes in measures of risk factors, atheroma burden, and vascular dimensions were compared by analysis of covariance, after controlling for baseline values, and expressed as least squared mean ± SE. A two-sided p-value <0.05 was considered statistically significant. All statistical analyses were performed with SAS version 9.1 (SAS Institute, Cary, North Carolina).

3.3. Results

3.3.1. Patient characteristics, medication use and risk factor control

The baseline characteristics and medication use of PAD and non-PAD patients are outlined in Table 3.1. The groups were matched for age and gender. The PAD patients had a greater history of hypertension (91.7% vs 77.5%, p=0.03), and were more likely to smoke (48.6% vs 24.6%, p=0.003). Otherwise, both groups had a comparable body mass index, history of diabetes, hyperlipidaemia, heart failure, myocardial infarction, and stroke. The baseline and concomitant medication use of statins, beta-blockers, aspirin, and angiotensin-converting enzyme (ACE) inhibitors were similar. Regarding the GLAGOV cohort, there were comparable numbers of PAD and non-PAD patients receiving placebo and evolocumab lipid-lowering therapy. The risk factor control at baseline and during study follow-up are summarised in Table 3.2. There was a lower baseline DBP (73.8 ± 13.3 mmHg vs 77.2 ± 10.2 mmHg, p=0.05), average follow-up DBP (73.6 ± 11.6 mmHg vs 77.3 ± 9.6 mmHg, p=0.02), and higher median follow-up hs-CRP (2.4 mg/L [1.5, 5.3] vs 1.4 mg/L [0.7, 2.9], p=0.005) in PAD compared to non-PAD patients. The risk factors were similar at baseline and during follow-up.

Table 3.1: Characteristics and medication use

Parameter (N, %)	Non-PAD (N = 240, 83.3%)	PAD (N = 48, 16.7%)	p value
Age, mean ± SD	60.1 ± 9.5	60.1 ± 9.6	
Female	70 (29.2)	14 (29.2)	1.00
Caucasian	232 (96.7)	46 (95.8)	0.68
Current Smoker	49 (24.6)	18 (48.6)	0.003
BMI, mean ± SD	28.7 ± 4.8	29.7 ± 5.7	0.21
History			
Hypertension	186 (77.5)	44 (91.7)	0.03
Diabetes	35 (14.6)	9 (18.8)	0.46
Hyperlipidaemia	190 (79.2)	35 (72.9)	0.34
Heart failure	10 (4.2)	2 (4.2)	1.00
Myocardial infarction	65 (27.1)	13 (27.1)	1.00
Stroke	3 (1.3)	0 (0.0)	1.00
Baseline medication use			
Statin	178 (74.2)	34 (70.8)	0.63
Beta blockers	180 (75.0)	33 (68.8)	0.37
Aspirin	217 (90.4)	41 (85.4)	0.30
ACE inhibitors	130 (54.2)	19 (39.6)	0.07
Concomitant medication use			
Statin	239 (99.6)	48 (100.0)	1.00
Beta blockers	184 (76.7)	36 (75.0)	0.80
Aspirin	218 (90.8)	42 (87.5)	0.43
ACE Inhibitors	129 (53.8)	22 (45.8)	0.32
Treatment Group for GLAGOV (N = 110)			0.55
Placebo	48/ 92 (52.2)	8 /18 (44.4)	
Evolocumab	44/ 92 (47.8)	10 /18 (55.6)	

Age and body mass index expressed as mean ± standard deviation. Other values are expressed as N (%). ACE, angiotensin-converting enzyme; BMI, body mass index; GLAGOV, Global assessment of plaque regression with a PCSK9 antibody as measured by intravascular ultrasound trial; PAD, peripheral artery disease

Table 3.2: Risk factor control

Parameter	Non-PAD (N = 240)	PAD (N = 48)	p value
LDL-C			
Baseline, mg/dL	112.3 ± 33.0	104.7 ± 26.4	0.14
Follow-up, mg/dL	64.4 ± 28.6	60.7 ± 24.3	0.41
Percent change	-39.8 ± 29.4	-39.0 ± 27.7	0.87
HDL-C			
Baseline, mg/dL	45.5 ± 12.1	43.5 ± 10.5	0.29
Follow-up, mg/dL	50.1 ± 12.8	48.1 ± 11.2	0.33
Percent change	11.2 ± 17.0	12.2 ± 18.8	0.72
Triglycerides			
Baseline, mg/dL	145.6 ± 73.5	148.1 ± 73.7	0.90
Follow-up, mg/dL	129.4 ± 54.0	131.9 ± 56.3	0.70
Percent change	-1.6 ± 38.2	-2.8 ± 32.2	0.79
Hs-CRP			
Baseline, mg/L	1.7 (0.8, 3.3)	2.8 (1.2, 4.2)	0.11
Follow-up, mg/L	1.4 (0.7, 2.9)	2.4 (1.5, 5.3)	0.005
Percent change	60.0 ± 355.7	61.3 ± 175.1	0.09
Systolic blood pressure			
Baseline, mmHg	130.6 ± 17.3	131.1 ± 20.1	0.86
Follow-up, mmHg	131.5 ± 16.9	133.9 ± 18.7	0.40
Percent change	1.8 ± 14.3	3.6 ± 16.8	0.43
Diastolic blood pressure			
Baseline, mmHg	77.2 ± 10.2	73.8 ± 13.3	0.05
Follow-up, mmHg	77.3 ± 9.6	73.6 ± 11.6	0.02
Percent change	1.2 ± 14.5	1.4 ± 17.4	0.93

Values expressed as mean ± standard deviation or median (interquartile range)

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Hs-CRP, high-sensitivity C-reactive protein

3.3.2. Baseline atherosclerotic plaque features and progression

The baseline atherosclerotic plaque volume and vessel wall measurements are described in Table 3.3. The PAD patients had smaller vessel (EEM) (253.5 ± 72.1 mm^3 vs 307.4 ± 103.7 mm^3, p=0.001) and lumen volumes (408.1 ± 111.6 mm^3 vs 486.9 ± 159.7 mm^3, p=0.001). People with PAD had lower TAV (154.6 ± 62.2 mm^3 vs 179.6 ± 74.1 mm^3, p=0.03) but had similar PAV (37.5 ± 8.2% vs 36.5 ± 8.7%, p=0.45) and calcium (33.1 ± 22.8% vs 26.7 ± 21.9%, p=0.06), compared with the non-PAD group. The annualised change in atheroma was calculated after adjusting for baseline plaque (see Table 3.4). There was no significant difference in the annualised change in EEM volume, lumen volume, PAV, and TAV between groups. The annualised change in PAV did not regress or progress (mean change -0.08%, 95% CI, -0.69 to 0.53, p=0.79; mean change -0.29%, 95% CI, -0.76 to 0.18, p=0.23) for PAD and non-PAD patients. There was significant regression in annualised TAV in non-PAD (mean change -3.50 mm^3, 95% CI, -6.19 and -0.80, p=0.01), but not in PAD (mean change -1.83 mm^3, 95% CI, -5.33 to 1.66, p=0.30). The proportion of people that had PAV progression (14.6% vs 19.6%, p=0.42) and regression (25.0% vs 35.4%, p=0.16) were similar for PAD and non-PAD patients, respectively (see Table 3.5). Calcification did not significantly differ during follow-up (35.7 ± 24.8% vs 29.4 ± 22.9%, p=0.06).

Table 3.3: Baseline atherosclerotic plaque and vessel wall measurements

Risk factor	Non-PAD (N = 240)	PAD (N = 48)	p value
EEM volume, mm^3	307.4 ± 103.7	253.5 ± 72.1	0.001
Lumen volume, mm^3	486.9 ± 159.7	408.1 ± 111.6	0.001
PAV, %	36.5 ± 8.7	37.5 ± 8.2	0.45
TAV, mm^3	179.6 ± 74.1	154.6 ± 62.2	0.03
Calcium, %	26.7 ± 21.9	33.1 ± 22.8	0.06

Values expressed as mean ± standard deviation. EEM, external elastic membrane; PAV, percent atheroma volume; TAV, total atheroma volume

Table 3.4: Annualised change in atheroma burden in PAD and non-PAD patients after adjusting for baseline plaque measurements

Parameter	Non-PAD (N = 240)			PAD (N = 48)			
	Mean ± SD	95% CI	p value in group	Mean ± SD	95% CI	p value in group	p value for interaction
EEM, mm^3	-4.40 ± 2.28	(-2.92, 1.93)	0.06	-2.33 ± 3.67	(-5.64, 5.00)	0.53	0.56
Lumen, mm^3	-0.49 ± 1.23	(-8.89, 0.09)	0.69	-0.32 ± 2.70	(-9.55, 4.90)	0.91	0.95
PAV, %	-0.29 ± 0.24	(-0.76, 0.18)	0.23	-0.08 ± 0.31	(-0.69, 0.53)	0.79	0.40
TAV, mm^3	-3.50 ± 1.37	(-6.19, -0.80)	0.01	-1.83 ± 1.78	(-5.33, 1.66)	0.30	0.24

Abbreviations as per Table 3.3. Lumen and EEM parameters were measured volumes.

Table 3.5: PAV progression, regression and change in calcium

Parameters	Non-PAD (N = 240)	PAD (N = 48)	p value
Progression	47 (19.6)	7 (14.6)	0.42
Regression	85 (35.4)	12 (25.0)	0.16
Calcium, %	29.4 ± 22.9	35.7 ± 24.8	0.06

Calcium is expressed as mean percentage ± standard deviation. The other values are expressed as N (%).

3.3.3. Plaque progression in PAD and non-PAD according to risk factor control

Annualised changes in PAV and TAV according to risk factor control are summarised in Table 3.6 and 3.7. The average change in PAV was comparable for PAD and non-PAD patients, when they achieved optimal LDL-C, HDL-C, triglycerides, SBP, DBP, hs-CRP, smoking abstinence, and more optimal risk factor control. More optimal risk factor control (mean difference -3.89, 95% CI, -7.35 to -0.42, p=0.03) and optimal triglycerides (mean difference -3.69, 95% CI, -7.04 to -0.34, p=0.03) was associated with more TAV regression in non-PAD than PAD patients, respectively. There were no significant differences in TAV change for control of LDL-C, HDL-C, SBP, DBP, hs-CRP, and smoking abstinence.

The PAD patients achieving LDL-C, HDL-C, triglycerides, SBP, DBP, hs-CRP, smoking abstinence or more optimal risk factor control, had a similar annualised change in PAV and TAV, compared to PAD patients that did not.

Table 3.6: Change in annualised percent atheroma volume after adjusting for baseline plaque measurements and according to risk factor control

	Non-PAD	PAD			
Risk factor	PAV change, % [mean ± S.E.]	PAV change, % [mean ± S.E.]	Mean difference (95% CI)	P-value in group	P-value for interaction
LDL-C					
<70 mg/dL	-0.43 ± 0.25	-0.18 ± 0.35	-0.26 (-0.86, 0.35)	0.41	0.87
≥70 mg/dL	-0.03 ± 0.27	0.14 ± 0.43	-0.17 (-0.97, 0.63)	0.68	
HDL-C					
>40 mg/dL	-0.21 ± 0.25	0.04 ± 0.35	-0.25 (-0.82, 0.32)	0.39	0.99
≤40 mg/dL	-0.55 ± 0.31	-0.31 ± 0.48	-0.24 (-1.18, 0.70)	0.61	
Triglycerides					
<150 mg/dL	-0.35 ± 0.25	0.02 ± 0.35	-0.37 (-0.95, 0.22)	0.22	0.40
≥150 mg/dL	-0.14 ± 0.29	-0.22 ± 0.45	0.08 (-0.78, 0.95)	0.85	
SBP					
<130 mmHg	-0.42 ± 0.26	-0.15 ± 0.40	-0.27 (-0.99, 0.45)	0.46	0.88
≥130 mmHg	-0.18 ± 0.25	0.02 ± 0.37	-0.19 (-0.86, 0.47)	0.56	
DBP					
<80 mmHg	-0.25 ± 0.26	0.05 ± 0.34	-0.30 (-0.87, 0.27)	0.31	0.59
≥80 mmHg	-0.34 ± 0.28	-0.35 ± 0.49	0.00 (-0.93, 0.94)	0.99	
Hs-CRP					
<2 mg/L	-0.31 ± 0.42	0.33 ± 0.53	-0.64 (-1.39, 0.12)	0.10	0.14
≥2 mg/L	-0.32 ± 0.43	-0.51 ± 0.54	0.19 (-0.61, 1.00)	0.64	
Smoking					
No	-0.36 ± 0.38	0.10 ± 0.52	-0.46 (-1.23, 0.31)	0.24	0.29
Yes	-0.19 ± 0.42	-0.33 ± 0.51	0.14 (-0.67, 0.95)	0.73	
RF Control					
More optimal	-0.35 ± 0.27	0.20 ± 0.37	-0.55 (-1.16, 0.06)	0.08	0.04
Less optimal	-0.08 ± 0.33	-0.78 ± 0.51	0.70 (-0.28, 1.69)	0.16	

Measurements adjusted for baseline percent atheroma volume. More optimal risk factor control was 4 or more specified risk factor targets achieved. Less optimal risk factor control was 3 or less risk factor targets achieved. DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Hs-CRP, high-sensitivity C-reactive protein; PAV, percent atheroma volume; RF, risk factor; SBP, systolic blood pressure

Table 3.7: Change in annualised total atheroma volume according to risk factor control after adjusting for baseline plaque measurements

	Non-PAD	PAD			
Risk factor	TAV change, mm^3 [mean ± S.E.]	TAV change, mm^3 [mean ± S.E.]	Mean difference (95% CI)	p value in group	p value for interaction
LDL-C					
<70 mg/dL	-4.23 ± 1.37	-1.60 ± 1.98	-2.63 (-6.12, 0.86)	0.14	0.36
≥70 mg/dL	-2.26 ± 1.50	-2.31 ± 2.45	0.05 (-4.57, 4.67)	0.98	
HDL-C					
>40 mg/dL	-3.37 ± 1.41	-1.81 ± 1.97	-1.57 (-4.83, 1.69)	0.35	0.87
≤40 mg/dL	-3.95 ± 1.74	-1.83 ± 2.73	-2.11 (-7.51, 3.28)	0.44	
Triglycerides					
<150 mg/dL	-4.15 ± 1.39	-0.46 ± 1.97	-3.69 (-7.04, -0.34)	0.03	0.03
≥150 mg/dL	-1.87 ± 1.61	-4.61 ± 2.54	2.74 (-2.15, 7.62)	0.27	
SBP					
<130 mmHg	-4.33 ± 1.54	-1.11 ± 2.34	-3.22 (-7.39, 0.94)	0.13	0.32
≥130 mmHg	-2.79 ± 1.50	-2.41 ± 2.14	-0.38 (-4.14, 3.38)	0.84	
DBP					
<80 mmHg	-4.13 ± 1.46	-1.24 ± 1.98	-2.90 (-6.20, 0.41)	0.09	0.22
≥80 mmHg	-2.39 ± 1.58	-3.33 ± 2.77	0.94 (-4.28, 6.16)	0.72	
Hs-CRP					
<2 mg/L	-2.25 ± 1.94	1.20 ± 2.72	-3.46 (-7.80, 0.89)	0.12	0.26
≥2 mg/L	-2.76 ± 2.03	-2.87 ± 2.72	0.11 (-4.46, 4.68)	0.96	
Smoking					
No	-2.29 ± 1.67	1.23 ± 2.56	-3.53 (-7.87, 0.81)	0.11	0.29
Yes	-3.05 ± 1.94	-2.93 ± 2.53	-0.12 (-4.75, 4.51)	0.96	
RF Control					
More optimal	-3.95 ± 1.28	-0.07 ± 1.95	-3.89 (-7.35, -0.42)	0.03	0.03
Less optimal	-0.32 ± 1.67	-3.56 ± 2.73	3.24 (-2.29, 8.77)	0.25	

Measurements adjusted for baseline total atheroma volume. Abbreviations as per table 3.5.

3.4. Discussion

This study investigated the basis for the high rates of MACE in PAD that were described in chapter two. A conventional explanation is that coronary artery disease with concomitant PAD reflects a high-risk vascular phenotype as this relates to plaque. The PAD participants in this study appeared to have early atherosclerosis with negative remodelling. On most IVUS measures, these patients had comparable plaque burden and progression to individuals without PAD. There was some evidence that non-PAD patients benefitted more from multiple risk factor control than in PAD, consistent with the clinical observations of the ACCELERATE cohort. There was no significant association between risk factor control and coronary artery plaque progression in PAD. These findings do not negate the importance of risk factor modification, although, they do underscore the resilience of coronary artery disease to standard medical treatments.

The PAD patients were more likely to receive guideline-recommended therapies and achieve risk factor control than the populations that have been previously researched [10, 12, 150]. The follow-up LDL-C, HDL-C, triglycerides and diastolic blood pressures were optimal when evaluated as a cumulative average. Aspirin and a statin were frequently prescribed. In contrast, an audit of PAD clinic visits in the United States found the uses of an antiplatelet, statin, and ACE inhibitor (or angiotensin 2 receptor blockers) were 36%, 33%, and 28%, accordingly [12]. In chapter two, we proposed that hs-CRP control would be a necessary strategy for reducing MACE. Here, hs-CRP and smoking were the least well-controlled risk factors. In general, this data provided an opportunity to study another well-managed PAD group, compared to other observational studies.

The PAD patients had a smaller EEM and lumen volume, but similar PAV to the non-PAD group. These findings may indicate constrictive (negative) remodelling. Atherosclerosis

is a dynamic pathophysiological process, where the arterial wall can expand or contract. Constrictive remodelling is characterised by early luminal stenosis and ischaemia. Prior studies of coronary artery disease have described an association between constrictive remodelling and stable angina presentations. Alternatively, expansive (positive) remodelling is a mechanism, whereby, the luminal area remains relatively preserved. Expansive remodelling has been linked with acute plaque rupture in the coronary circulation [174]. However, few studies have evaluated remodelling in lower extremity arteries. PAD is typically manifested by intermittent claudication and critical limb ischaemia. We postulate that these patients have a predilection for constrictive remodelling in the peripheries, as was evident here in the coronary circulation.

Prior studies that have investigated coronary artery plaque in PAD have been limited. The more substantial part of this research was cross-sectional and did not account for contemporary risk factor control [166-168]. Hussein *et al.* showed that PAD-affected individuals had greater coronary atherosclerotic burden and progression than non-PAD patients [152]. However, this was a univariate comparative analysis. Questions remain as to whether differences in demographics and risk factor control could explain these observations. Central to this issue is the relationship between risk factors and PAD, compared to other atherosclerotic conditions. Smoking has a more substantial role in the development of PAD, whereas hypertension and elevated LDL-C have a modest association when contrasted with coronary artery disease [1, 15-17]. If we reconcile previous studies with our analysis, PAD patients have more comorbidities that are associated with high-risk coronary artery plaque. We propose that PAD is occurring in more complex patients, as this relates to an older age, elevated inflammation, smoking and poorly controlled diabetes.

Several caveats should be noted regarding this exploratory analysis. There were limitations in the sample size, thereby making it difficult to make any definite conclusions. A single specified arterial segment was examined, where other arteries could have different

atherosclerotic morphologies. Serial IVUS imaging was used to assess the volume of plaque, calcium, and vessel size, although other plaque features that relate to inflammatory composition and arterial remodelling were not assessed. While the PAD and non-PAD groups were comparable across various baseline characteristics, there were some differences in smoking, hypertension, and inflammatory control. As this analysis was observational, the potential for unmeasured confounders cannot be excluded. This data was derived from three prior clinical trials of intensive lipid-lowering, whereas other risk factor interventions were not explicitly implemented. The duration of risk factor control preceding the commencement of study could vary between participants. In investigating the effects of multiple risk factor control, a more extended follow-up could be worthwhile. Long-term studies of multiple risk factor control in diabetes, suggest that the observable impact on MACE can be delayed [134]. Nevertheless, this study provided a unique longitudinal examination of coronary artery atherosclerosis in a setting where risk factors were assessed comprehensively. Participants were not routinely screened for PAD, and they underwent coronary angiography for a clinically indicated reason. Therefore, these findings do not necessarily reflect other situations of bystander PAD or coronary artery disease, that is more clinically quiescent. Despite these limitations, there are few analyses of this kind in PAD, partly due to the challenges of performing multiple invasive procedures on people in a clinical trial.

3.5. Conclusions

Patients with concomitant PAD did not exhibit more significant coronary artery disease burden or progression, as is commonly accepted. There was no observed impact of individual and multiple risk factor control on plaque progression, suggesting resilience to current treatments. More research is needed into the interaction with coronary artery atherosclerosis in PAD

patients, to understand better why they experience such high rates of MACE. Studies that use serial IVUS imaging could provide new perspectives into treatment strategies.

CHAPTER 4: GENDER DIFFERENCES IN LONG-TERM MORTALITY AND MAJOR ADVERSE CARDIOVASCULAR EVENTS IN PAD – A META-ANALYSIS

ABSTRACT

Background and aims: Individual studies in peripheral artery disease (PAD) indicate that there are gender discrepancies in symptoms, functional status, and treatment utilisation. It remains uncertain whether this translates to different long-term outcomes. We examine potential gender differences in mortality and major adverse cardiovascular events (MACE) in PAD.

Methods: PubMed and Embase databases were searched for studies between 2000 until January 2019. After a review of 13,582 citations, fourteen articles were analysed. The reported age-adjusted hazard ratios (HR) for gender differences in mortality and MACE were included for meta-analysis.

Results: Male gender was associated with a greater risk of all-cause mortality (HR 1.13, 95% CI 1.10 to 1.16, p<0.001) and MACE (HR 1.10, 95% CI 1.06 to 1.14, p<0.001). In a sensitivity analysis, male gender was associated with higher mortality risk for patients presenting with either critical limb ischaemia (HR 1.08, 95% CI 1.05 to 1.10, p<0.001) or mixed clinical presentations (HR 1.16, 95% CI 1.11 to 1.21, p<0.001), but not for those with intermittent claudication (HR 1.13, 95% CI 0.98 to 1.30, p=0.09). Elevated mortality risk was evident following revascularisation (HR 1.11, 95% CI 1.04 to 1.19, p=0.003), hospitalisation (HR 1.15, 95% CI 1.08 to 1.22, p<0.001), and amputation (HR 1.09, 95% CI 1.08 to 1.10, p<0.001), although not in outpatient clinics (HR 1.13, 95% CI 0.97 to 1.32, p=0.13), in males compared with females.

Conclusions: Greater mortality and MACE rates in men with PAD occurred despite other accepted gender disparities. The mechanism underlying these gender differences in outcomes for PAD patients requires further investigation.

4.1. Introduction

Peripheral artery disease (PAD) is associated with substantial morbidity and mortality. While coronary artery disease and cerebrovascular disease are the most common causes of death (40-60% and 10-20%, respectively) in PAD patients, 20-30% of patients are likely to die from non-cardiovascular causes [6]. PAD has been traditionally studied as a disease affecting males. However, the true gender-specific prevalence is unclear, as many cases are clinically silent. It has been observed that PAD in females is less frequent than in age-matched males, but the total burden, in terms of the number of affected individuals is higher [140, 175, 176]. Studies have demonstrated gender discrepancies in clinical symptoms, functional status, and quality of life for patients with PAD [140-142]. Females are more likely to be asymptomatic or have atypical symptoms, further challenging clinical diagnosis [175, 176]. PAD is associated with more walking impairment and progressive functional decline in women [141]. Research into gender differences in the prescription of medical and lifestyle therapies for PAD is lacking. However, there is broad evidence in the cardiovascular setting that females are treated less intensively to achieve cardiovascular risk factor targets [177]. With gender disparities in clinical features and practices, there is potential for a vast divergence in long-term outcomes for PAD.

While adjustment for age has been found to abate the reported long-term gender differences in mortality after myocardial infarction [178], PAD has been less well studied. Scientific statements have increasingly promoted the need for increased awareness and further research into gender-specific concerns in PAD. Women are consistently under-represented in clinical trials in this space [140], and accordingly, it is difficult to draw too many conclusions from individual studies. This study examined the impact of gender on all-cause mortality and major adverse cardiovascular events (MACE) in symptomatic PAD.

4.2. Methods

4.2.1. Search strategy

A digital search was conducted on PubMed and Embase databases for studies in the English language between the 1st January 2000 and 10th January 2019. Articles before the 1st January 2000 were not included, to reflect modern clinical trends, such as the emerging use of statins and other advances in risk factor control. The following terms were searched in the titles and abstracts of articles: ("peripheral arterial disease" or "peripheral artery disease" or "peripheral vascular disease" or "peripheral arterial occlusive" or "claudication" or "claudicant" or "ankle brachial ind" or "critical limb" or "amputation" or "lower limb" or "lower extremity") and ("mortality" or "death" or "survival" or "cardiovascular event" or "myocardial infarction" or "acute coronary syndrome" or "stroke" or "cerebrovascular event" or "CVA"). This broad approach was not restricted by gender-related terms, to find all relevant studies, even those not primarily focused on gender. That process was the basis for finding all the included studies. For completion, a manual search of abstracts was made for PAD studies that contained gender terms, such as "gender" and "women". The study protocol was prospectively registered with the PROSPERO international register (CRD42018110144) and fully adhered to the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). An example search strategy is presented in the supplemental material.

4.2.2. Eligibility criteria

Only studies of symptomatic PAD were included, and this was characterised as any one of the following: intermittent claudication or a diagnosis of symptomatic PAD, critical limb ischaemia, a PAD revascularisation procedure, a lower limb amputation for PAD, or hospitalisation for PAD. Thus, randomised clinical trials of symptomatic PAD, as well as

observational analyses of PAD interventions and hospitalisations were eligible, while population studies of ankle-brachial index screening were not. For inclusion, these studies also had to: (1) report a hazard ratio (HR) with 95% confidence interval (95% CI) for gender-specific all-cause mortality or major adverse cardiovascular events (3-point composite of myocardial infarction, stroke and mortality); (2) have a follow-up duration of 12 months or more.

Studies were excluded if the: (1) reported hazard ratio did not adjust for age as a covariate; (2) PAD was not distinguished from other conditions such as diabetic foot syndrome, coronary artery disease or abdominal aortic aneurysm; (3) article was published before 1st January 2000; (4) cohort was followed from before 1st January 1990; (5) sample size was less than 1000. Only all-cause mortality and a 3-point MACE composite endpoint were considered. Where multiple studies described the same population, the study with the most comprehensive gender analysis was included. If a study provided a range of follow-up periods, analysis of the longest duration was used. Individual definitions of endpoints were included in the supplemental material.

4.2.3. Data extraction and quality assessment

Data extraction and quality assessment were conducted by two independent authors using the predefined eligibility criteria. Where there were any differences, a third reviewer was consulted. Information was transcribed into a spreadsheet. Details recorded were the: study design; length of follow-up; baseline demographics and risk factors; definition of PAD; a history of lower limb revascularisation; type of statistical analyses and covariate adjustment; hazard ratio; and 95% confidence intervals. Outcomes were defined in terms of long-term

MACE and all-cause mortality. The study quality was assessed using the Newcastle Ottawa Scale [179].

4.2.4. Study aims

The primary endpoint was an examination of gender differences in long-term mortality using the multivariate-adjusted hazard ratio. The combined results were expressed as a hazard ratio for male versus a female reference group. A sensitivity analysis was performed to consider clinical presentation (intermittent claudication and critical limb ischaemia) and follow-up context (outpatient encounter, hospitalisation, revascularisation, and amputation). The secondary endpoint was a gender-specific multivariate-adjusted hazard ratio for MACE.

4.2.5. Statistical analysis

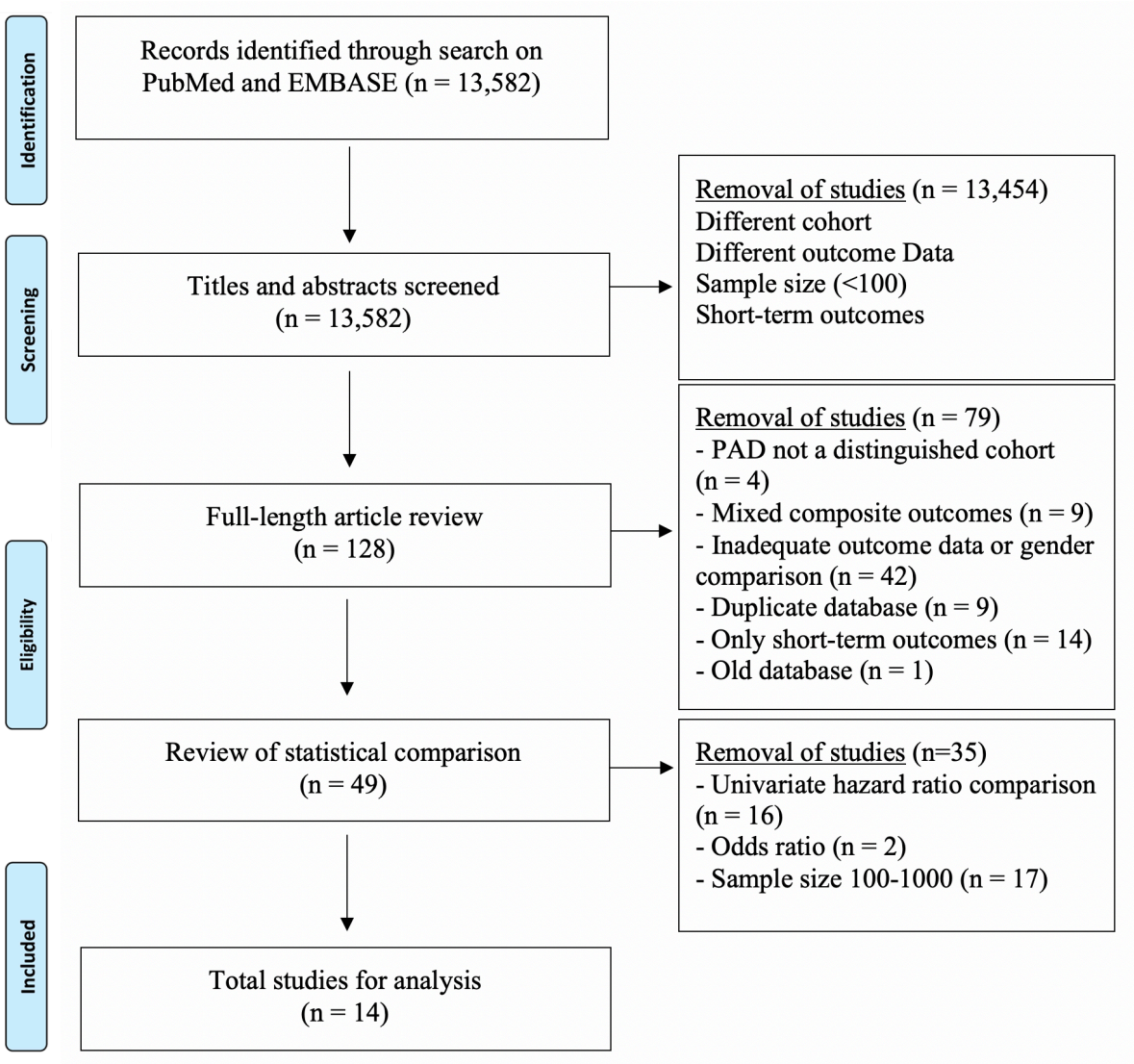
Statistical analysis was performed using Stata 14.1 and the metan suite of commands. Hazard ratios were examined on the log scale and transformed for graphical presentation, with 95% CI reported. Random effects modelling was used with the method of DerSimonian and Laird. Statistical heterogeneity was evaluated by the I^2 statistic and quantified as low (<25%), moderate (25-75%), or high (>75%). Sensitivity analysis was performed by clinical setting and patient diagnosis. Publication bias was assessed visually by funnel plots and statistically by the Egger and Begg test. The Duval and Tweedie's trim and fill method were also used to investigate publication bias. A two-sided p-value of <0.05 was considered significant.

4.3. Results

4.3.1. Search results

This search identified a total of 13,582 citations. There was a removal of 13,454 articles following the screening of titles and abstracts. A further 79 studies were excluded after full-length review. The remaining 49 articles reported a statistical comparison between gender groups. Fourteen studies were included for meta-analysis [30, 180-192]. The reasons for study exclusion are summarised in Figure 4.1. More information about the excluded studies with a small sample size (n=100 to 1000) and duplicate database is available in the supplemental material.

Figure 4.1: PRISMA diagram



The search process for studies included in the meta-analysis.

PAD, Peripheral artery disease; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses

4.3.2. Study quality and bias assessment

There was significant heterogeneity in study inclusion, study design, treatment, follow-up duration, and statistical analysis. The study quality was assessed using the Newcastle-Ottawa scale (Table 4.1). Of the fourteen studies included in this review, six articles had a specific focus on gender differences in PAD [182, 184-187, 190]. Eight studies used an administrative dataset [30, 181, 183, 185, 187, 188, 191, 192], five examined a hospital or community cohort [180, 182, 184, 186, 190], and one used a randomised controlled trial [189]. A summary of study inclusion, primary endpoints, MACE definition, study characteristics and funnel plot analysis is in the supplemental material. No significant statistical bias was demonstrated on the Egger and Begg test for small-study effects (p=0.18). Duval and Tweedie's trim and fill method did not alter overall summary point estimates.

4.3.3. Study characteristics and event rates

The study characteristics and events rates are summarised in Table 4.1. The studies were published between 2003 and 2018. The sample size range was between 1,404 and 218,858 total subjects. Females represented 47.4% of the studied population. The mean follow-up for all studies was 46 ± 21 months, expressed as a mean ± standard deviation. The range of follow-up periods was between 12 and 77 months. Where each study was equally weighted, the incidence of mortality during follow-up was 50% or an annual event rate of 13%. Five studies examined MACE [180, 182, 183, 187, 190], and the average total incidence of MACE during follow-up was 45%. Two studies began following a vascular clinic review and not specifically relating to a PAD intervention or hospitalisation [183, 187]. Five articles provided details of baseline characteristics and treatment in men and women. The females had a higher mean age than males (71 ± 2 and 68 ± 4, respectively). There was a higher prevalence of smoking and coronary

artery disease in men, whereas hypertension was more common in women. Intermittent claudication was a more frequent clinical presentation in males.

Table 4.1: Characteristics of included studies

AUTHOR	YEAR	DX	DATES	LOCATION	DATABASE	TYPE	CONTEXT	NOS
ABTAN [180]	2017	IC, CLI	2003-2008	INTERNATIONAL	REACH	PROSP	HOSPIT	8
AL-OMRAN [181]	2003	IC, CLI	1991-1998	CANADA	CANADIAN INSTITUTE OF HEALTH INFO	RETRO	REVASC	8
BUDTZ-LILLY [182]	2015	IC, CLI	2000-2007	DENMARK	DANISH VASCULAR REGISTRY	RETRO	REVASC	8
CEA SORIANO [183]	2017	IC	2000-2010	UK	THE HEALTH IMPROVEMENT NETWORK	RETRO	OPD	9
DUFFY [184]	2014	IC, CLI	2003-2010	UK	VASCULAR STUDY GROUP OF ENGLAND	PROSP	REVASC	9
FREISINGER [185]	2018	IC, CLI	2009-2013	GERMANY	BARMER GEK	RETRO	HOSPIT	8
GROOTENBOER [186]	2011	IC, CLI	1993-2006	NETHERLANDS	ERASMUS CENTER	PROSP	REVASC	8
HUSSAIN [187]	2016	IC	2004-2007	CANADA	ONTARIO ADMINISTRATIVE DATASET	RETRO	OPD	9
JONES [30]	2013	CLI	2000-2008	US	CENTER FOR MEDICARE AND MEDICAIDE SERVICES	RETRO	AMPUT	8
MUSTAPHA [188]	2018	CLI	2010-2015	US	CENTER FOR MEDICARE AND MEDICAIDE SERVICES	RETRO	HOSPIT	9
SCHANZER [189]	2008	CLI	2001-2003	US/ CANADA	PREVENT III - RCT	PROSP	REVASC	9
SIGVANT [190]	2017	IC, CLI	2006-2013	SWEDEN	SWEDISH NATIONAL PATIENT REGISTER	RETRO	HOSPIT	8
TURLEY [191]	2017	IC, CLI	2010-2012	US	CENTER FOR MEDICARE AND MEDICAIDE SERVICES	RETRO	REVASC	9
VAARTJES [192]	2009	IC, CLI	1997-2000	NETHERLANDS	HOSPITAL DISCHARGE REGISTRY AND DUTCH POPULATION REGISTRY	RETRO	HOSPIT	8

CLI, critical limb ischaemia; DX, diagnosis; HOSPIT, hospitalisation; IC, intermittent claudication; NOS, Newcastle Ottawa Scale; OPD, outpatient; PROSP, prospective; RETRO, retrospective; REVASC, revascularisation

4.3.4. All-cause mortality

For the primary endpoint of all-cause mortality, thirteen studies incorporating 668,690 patients were evaluated (Figure 4.2 and Table 4.2). There was an increased risk of all-cause mortality for males (HR 1.13, 95% CI 1.10 to 1.16, p<0.001, I^2 88%). In nine studies, male gender was significantly associated with all-cause mortality, with a hazard ratio ranging between 1.06 (95% CI 1.04 to 1.08) and 1.36 (95% CI 1.21 to 1.53). For the remaining four studies, there was no statistically significant gender difference in all-cause mortality.

A sensitivity analysis was performed based on the clinical presentation and follow-up context of the observed cohort (Figure 4.3). Male gender was associated with increased all-cause mortality for patients with critical limb ischaemia (HR 1.08, 95% CI 1.05 to 1.10, p< 0.001, I^2 68%) and mixed clinical presentations (HR 1.16, 95% CI 1.11 to 1.21, p<0.001, I^2 83%), but not for those with intermittent claudication (HR 1.13, 95% CI 0.98 to 1.30, p=0.09, I^2 88%). All-cause mortality was higher in males for studies following revascularisation (HR 1.11, 95% CI 1.04 to 1.19, p=0.003, I^2 76%), hospitalisation (HR 1.15, 95% CI 1.08 to 1.22, p<0.001, I^2 93%) and amputation (HR 1.09, 95% CI 1.08 to 1.10, p<0.001), compared with females. There was no significant gender difference in all-cause mortality for studies following an outpatient encounter (HR 1.13, 95% CI 0.97 to 1.32, p=0.13, I^2 94%).

Figure 4.2: Relative risk estimates of all-cause mortality

Forest plot reporting the hazard ratios (HR) with 95% confidence interval of all-cause mortality in patients, with females as the reference group. Note that Duffy 2014 examined intermittent claudication (IC) and critical limb ischaemia (CLI) separately.

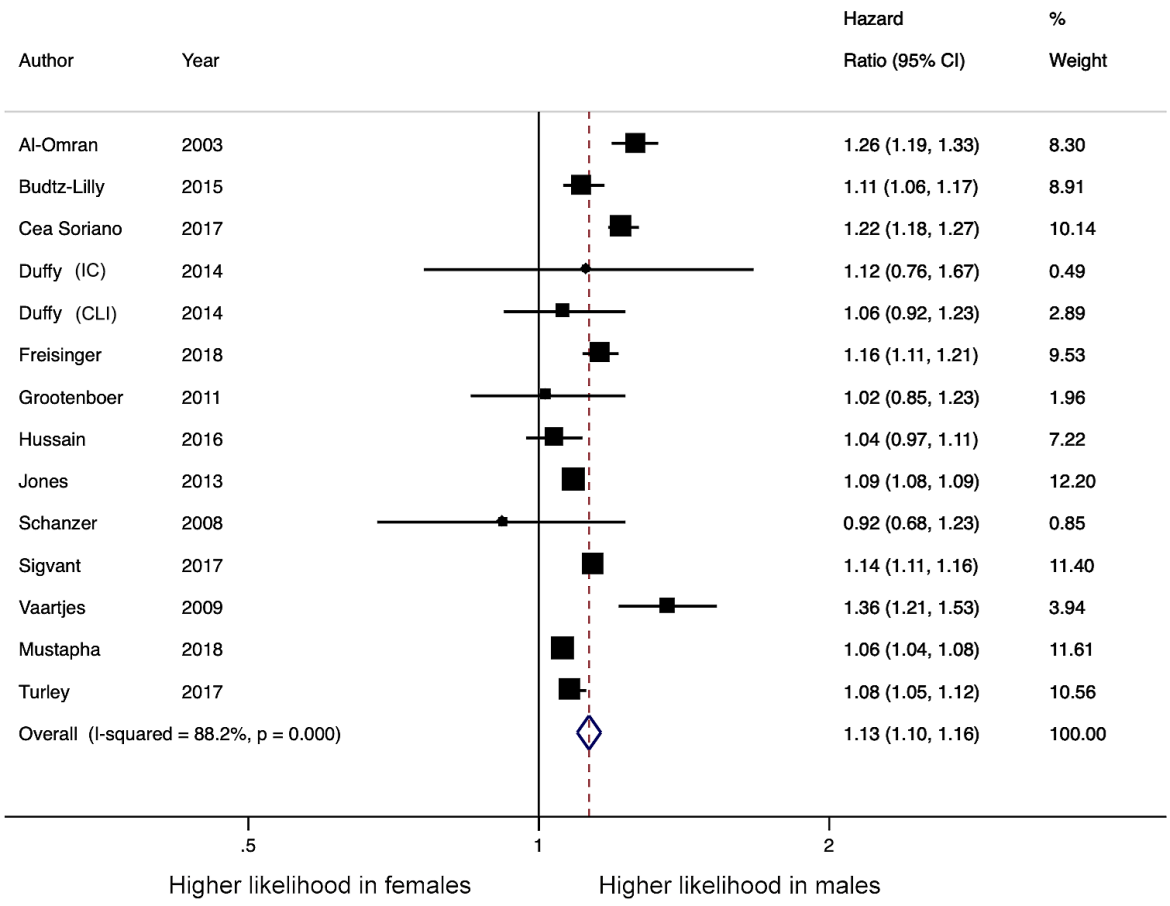


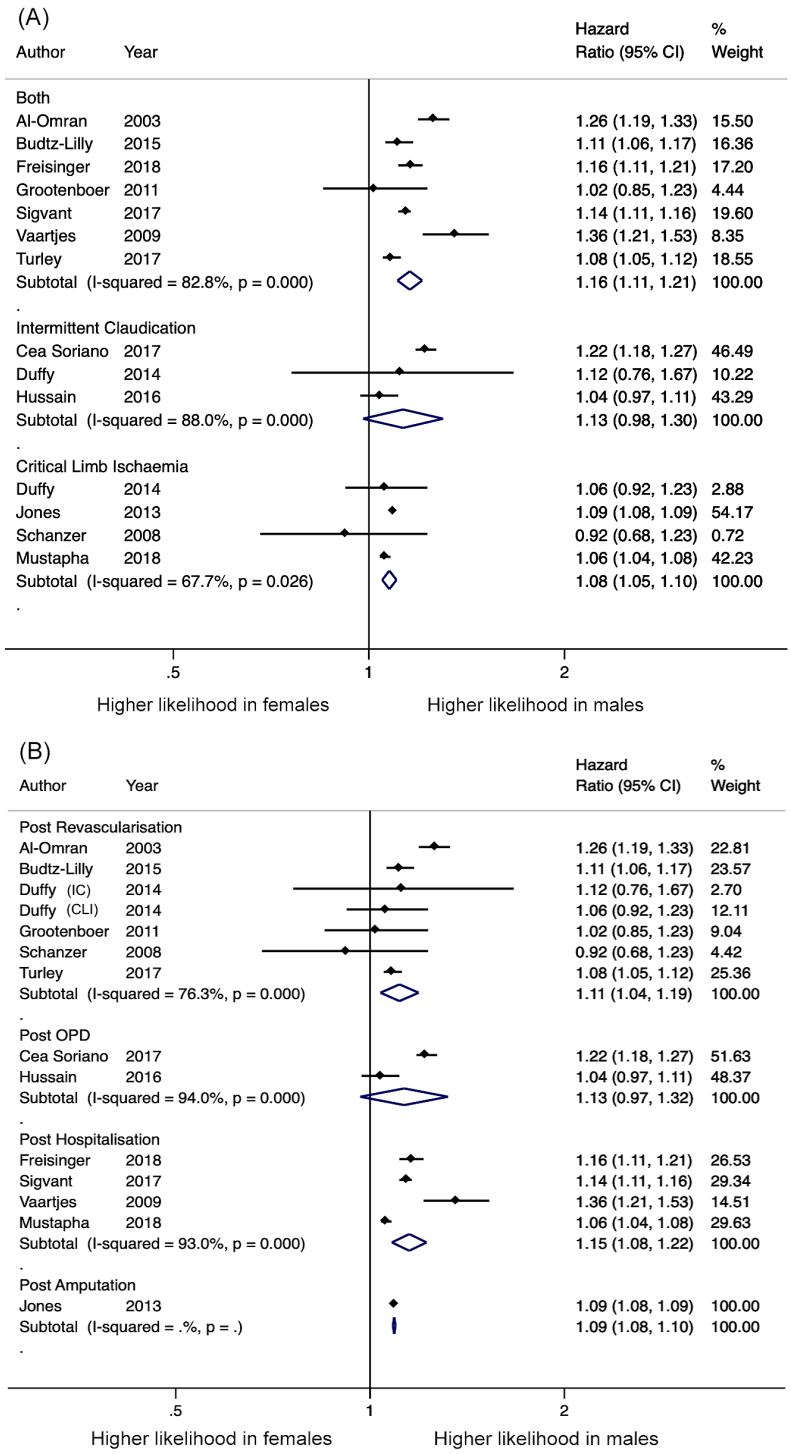
Table 4.2: Events and hazard ratios for all-cause mortality

AUTHOR	FU (MTHS)	CLI (%)	MALE (NO)	FEMALE (NO)	TOTAL EVENT	EVENT /YEAR (%)	HR (M:F)	95% CI	95% CI
AL-OMRAN, 2003	37.2	-	9874	4342	9732	12%	1.26	1.19	1.33
BUDTZ-LILLY, 2015	63.6	65%	6289	4945	6407	11%	1.11	1.06	1.17
CEA SORIANO, 2017	76.8	0%	17053	11431	16147	9%	1.22	1.18	1.27
DUFFY (IC), 2014	48	0%	515	197	-	-	1.12	0.76	1.67
DUFFY (CLI), 2014	48	100%	1233	631	-	-	1.06	0.92	1.23
FREISINGER, 2018	48	49%	23282	18591	-	-	1.16	1.11	1.21
GROOTENBOER, 2011	76.8	-	753	293	610	9%	1.02	0.85	1.23
HUSSAIN, 2016	64.8	0%	4454	2461	4120	11%	1.04	0.97	1.11
JONES, 2013	22.7	100%	89627	96711	132114	24%	1.09	1.08	1.09
MUSTAPHA, 2018	48	100%	37681	34518	38987	27%	1.06	1.04	1.08
SCHANZER, 2008	12	100%	897	507	234	17%	0.92	0.68	1.23
SIGVANT, 2017	33.6	-	34587	31602	39104	21%	1.14	1.11	1.16
TURLEY, 2017	12	22%	115170	103688	29702	14%	1.08	1.05	1.12
VAARTJES, 2009	60	-	2539	1619	1229	6%	1.36	1.21	1.53

Abbreviations: 95% CI, 95% confidence interval; CLI, critical limb ischaemia; FU, follow-up (months); HR, hazard ratio; NO, number; YR, year

Figure 4.3: Relative risk estimates of all-cause mortality based on situation

(A) clinical presentations, and (B) follow-up context. Forest plot reporting the hazard ratios (HR) with 95% confidence interval of all-cause mortality in patients, according to clinical presentation, with females as the reference group.



4.3.5. Major adverse cardiovascular events

Five included studies reported a multivariate-adjusted hazard ratio for MACE (Figure 4.4 and Table 4.3). There was a significant association for male gender and MACE (HR 1.10, 95% CI 1.06 to 1.14, p<0.001, I^2 53%). Male gender was significantly associated with increased MACE in three studies. In the two remaining studies, there was no significant gender discrepancy in MACE.

Figure 4.4: Relative risk estimates of major adverse cardiovascular events

Forest plot reporting the hazard ratios (HR) with 95% confidence interval of major adverse cardiovascular events in patients, with females as the reference group.

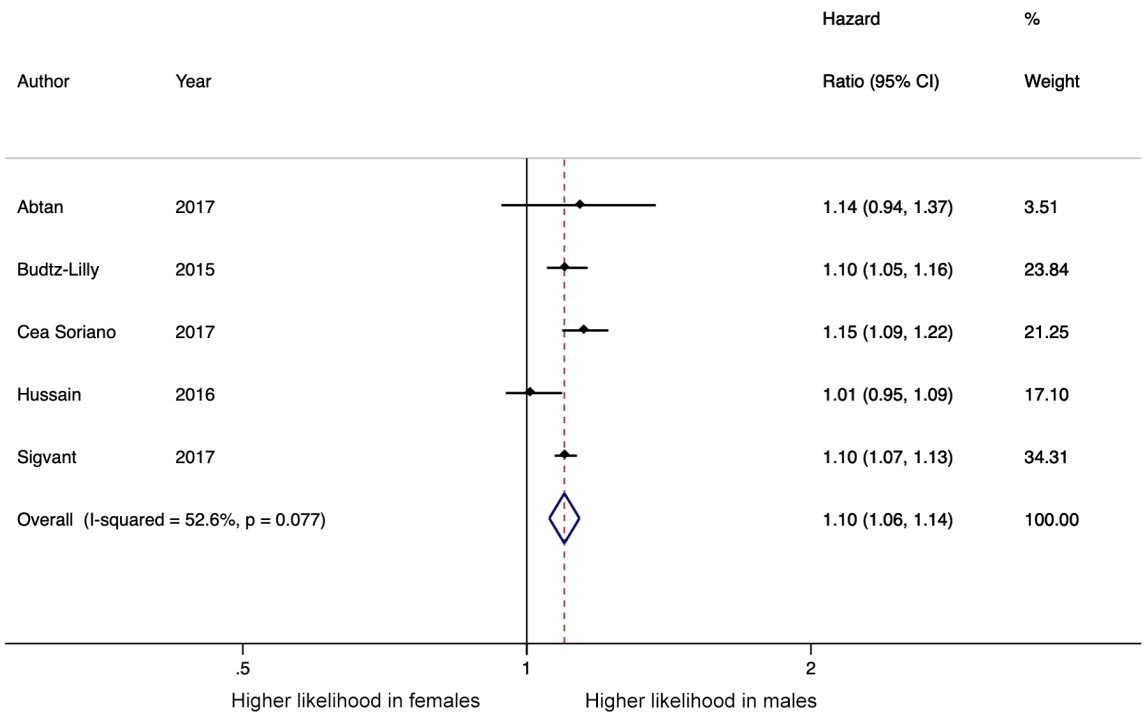


Table 4.3: Multivariate-adjusted hazard ratio for major adverse cardiovascular events

AUTHOR	FU	CLI (%)	MALE (NO)	FEMALE (NO)	TOTAL EVENT	EVENT /YR (%)	HR (M:F)	95% CI	95% CI
ABTAN, 2017	48	-	4156	1849	1057	4%	1.14	0.77	1.22
BUDTZ-LILLY, 2015	63.6	65%	6289	4945	7195	12%	1.10	1.05	1.16
CEA SORIANO, 2017	76.8	0%	17053	11431	5460	4%	1.15	1.09	1.22
HUSSAIN, 2016	64.8	0%	4454	2461	4504	12%	0.99	0.92	1.05
SIGVANT, 2017	33.6	-	34587	31602	30765	17%	1.10	1.07	1.13

95% CI, 95% confidence interval; CLI, critical limb ischaemia; F, female; FU, follow-up (months); HR, hazard ratio; M, male; NO, number; YR, year

4.4. Discussion

From a pooled result of thirteen studies, male gender was independently associated with a 13% relative increase in all-cause mortality in patients with PAD. With sensitivity analysis, this trend was consistent across different domains, where the clinical presentation and follow-up context was determined. The follow-up of patients ranged between 12 and 77 months. The incidence of mortality was high for both men and women and estimated at 13% each year when studies were equally weighted. Additionally, from a combination of five studies, the male gender was associated with a 10% increase in MACE. This secondary analysis suggested that the increased mortality in men may be at least partly attributable to cardiovascular-related events. These findings establish gender differences in long-term mortality and MACE among patients with symptomatic PAD and differ from coronary artery disease patients, in which age plays an important role in gender-related differences in clinical outcomes [178].

In order to understand why male gender correlated with increased mortality, the potential for unmeasured confounders should be considered. The multivariate regression analyses did not account for disease severity, psychosocial factors, some medical comorbidities, effects of medical and lifestyle therapies, and complications from lower extremity revascularisation, and these could explain the outcome differences [10, 28, 41, 63, 89, 193, 194]. Women had a higher mean age than men, and this was likely to correspond with variations in functional status and psychosocial factors. Social circumstances can impact patient compliance, and this is particularly important in PAD, where there is an emphasis on lifestyle modification [147]. While many studies adjusted for multiple cardiovascular risk factors and comorbidities, for others, the list was less comprehensive. Diabetes in females is more strongly associated with intermittent claudication and fatal coronary artery disease compared with males [177]. Therefore, differences in the prevalence of comorbidities, including diabetes, might explain the outcome discrepancies to a certain extent. In this

systematic review, a few studies reported a higher incidence of hypertension [182, 184-186] in women, whereas coronary artery disease [182, 184-186], diabetes [182, 185] and smoking [182, 184-186] were more common in men. Still, for those studies, their hazard ratios adjusted for these distinctions. The optimal control of these conditions might vary according to gender. In general, there continues to be less awareness and recognition of cardiovascular risk in women. Females receive less intensive treatment of hypertension and dyslipidaemia [195]. It could be that the diagnosis of PAD is a catalyst or "wake-up call" for change, although there is a paucity of substantiating evidence. The REACH registry was a prospective international study that followed 8,322 people with symptomatic PAD for up to four years. In that study, male gender was independently associated with optimal risk factor control, when compared with females (odds ratio 1.9) [10]. More observational research is needed to define how men and women with PAD are medically managed.

This meta-analysis evaluated MACE as a secondary outcome, as this is the leading cause of death for PAD patients [6]. Male gender was associated with higher age-adjusted mortality in PAD, unlike coronary artery disease [178], and this might point to a non-cardiac aetiology. Major adverse limb events commonly occur following lower extremity revascularisation [28] and could affect men and women discordantly. These outcomes, which can include acute or chronic limb-threatening ischaemia and lower limb amputation, are associated with a 3-fold increase in the 1-year mortality [31]. Some studies have shown how major adverse limb events contributed to higher mortality in men. Freisinger *et al.* examined an administrative dataset of 41,873 people undergoing lower extremity revascularisation. The authors performed propensity score matching to assess the effect of gender on in-hospital and long-term (4-year) outcomes. Despite comparable rates of many perioperative adverse events, male gender remained an independent risk factor for in-hospital and long-term incidence of amputation (HR 1.28, $p<0.001$) [185]. Similarly, Hess *et al.* investigated 1-year outcomes

following lower extremity revascularisation in 381,415 patients. Female gender was associated with less major adverse limb events [28]. These findings suggest that there are technical factors related to lower extremity revascularisation that may contribute to excess mortality in males. Patients with conservatively-treated intermittent claudication are unlikely to die from major adverse limb events [25]. This meta-analysis featured three studies of more stable PAD groups; and in these, there was still a trend for increased mortality in men [180, 183, 187]. So, while this meta-analysis focused on mortality and MACE, an investigation into potential gender differences in major adverse limb events would be of interest in future analyses.

The assessment of mortality according to the presentation and follow-up context gives further insight into the existing discrepancies and may adjust for significant group differences. Two studies in this meta-analysis reported more women with CLI than men [184, 185], which is meaningful, given the difference in prognosis between CLI and intermittent claudication [7]. PAD patients that undergo intervention or require hospitalisation are generally at higher risk than those seen in the clinic setting [28]. Here, the gender divergence in mortality was possibly greater in more advanced disease and after revascularisation. Prior research has suggested that men and women are selected differently for lower extremity revascularisation [140]. The sensitivity analysis of post-revascularisation studies found male gender to be associated with an 11% higher mortality risk, thereby accounting for differences in the use of these interventions.

From 1980 through 2000, there was a significant reduction in cardiovascular-related deaths, which was attributable to emerging medical therapies and advances in risk factor control [196]. During this era, gender disparities in heart disease gained increasing attention. Professional bodies have introduced initiatives to promote the awareness of cardiovascular disease in women. Over the subsequent decade, there was a notable improvement in clinical

outcomes [197]. In this meta-analysis, a focus was made on modern literature after the incorporation of health campaigns and medical therapies such as statins.

Most of the included studies were retrospective and used administrative datasets. In the examination of gender and mortality, the use of large administrative datasets is, in many ways, preferable to prospective clinical trials. It is expected that data regarding gender and mortality were reliably coded. Real-world datasets allow the evaluation of large numbers of individuals, which is better suited to review current practice than the confines of a clinical trial. Prospective clinical studies can be limited by enrolment bias, which is especially relevant, given that women are usually under-represented [140].

Several caveats should be noted. Gender was not the primary focal point of many included studies. The regression analysis in these articles might not have adequately adjusted for gender-related confounders. These studies did not assess disease severity, psychosocial factors, some medical comorbidities, effects of medical and lifestyle therapies, and complications from lower extremity revascularisation. Furthermore, there was significant heterogeneity across studies regarding disease severity, follow-up, treatment, and endpoint. There were differences in the covariates used in the regression model. However, sensitivity analysis discerned between the clinical presentations and types of follow-up and found a minimal impact on the pooled hazard ratio and 95% confidence interval. The descriptions of follow-up were characterised by how data was initially captured, although this had limitations. Studies following PAD hospitalisation did not differentiate between the interventions received. Also, over time, PAD patients will naturally crossover between revascularisation, amputation, hospitalisation, and clinic review. Nevertheless, a focus on the study context delineated between higher and lower-risk patients and accounted for group differences in revascularisation use. The initial search identified articles that featured more than 100 patients, but smaller studies (n=100-1,000) were subsequently excluded [99, 142, 198-210]. Those study findings,

as well as an overview of their quality, are summarised in the supplemental materials. The main reason for removing them was to avoid analysis bias. A vast body of research has evaluated mortality outcomes in PAD, but a considerable portion of smaller studies do not test for gender differences. The lack of gender comparisons in clinical trials is common and has been described [140, 211]. Less sizeable studies are possibly underreporting gender analysis because few events occur, and their findings are not significant. Their inclusion for meta-analysis has the potential to favour positive data. Hence, larger studies were chosen because gender-analysis was more consistently performed. There was no publication bias detected visually with funnel plot or statistically with the Begg and Egger testing. Of note, if these smaller studies had been added, they would have a modest weighting in the random-effects model of statistical analysis.

4.5. Conclusions

Male gender was associated with long-term MACE and mortality in symptomatic PAD. The gender discrepancies in mortality were evident across different clinical domains. This divergence was potentially greater in advanced disease, where there is critical limb ischaemia or a need for a lower extremity procedure. It remains to be seen whether this reflects clinical factors that are negatively affecting males or if this more relates to females that have benefitted from treatment. Notwithstanding, there were exceptionally high rates of MACE and mortality for both men and women, indicating an urgent need for new strategies. An evaluation of the attitudes and behaviours of clinicians and their patients with a gender-specific lens is required. Consideration for the effect of clinical variables on men and women could lead to more effective health initiatives that are attentive to both gender groups. There may be a role for PAD care delivery models that focus separately on men and women, as has been introduced in other aspects of cardiovascular medicine [212]. The increased mortality in men does not

minimise the importance of PAD in women. There are many female-predominant issues in PAD, including challenges with the clinical diagnosis; a lack of public and clinician awareness; under-representation of women in clinical trials; and possibly an under-utilisation of treatments, such as lower extremity revascularisation [140]. The association between male gender and mortality occurred despite these other disparities, and this paradox should be scrutinised to improve overall understanding of PAD.

4.6. Supplemental material

Table 4.4: Example search strategy (PubMed)

#	SEARCHES	RESULTS
1	Peripheral Arterial Disease [MH]	6263
2	Peripheral Arterial Disease* [TI]	3689
3	Peripheral Vascular Diseases [MH:NOEXP]	12406
4	Peripheral Vascular Disease* [TI]	2351
5	Peripheral arterial occlusive* [TI]	898
6	Intermittent Claudication [MH]	7711
7	Claudication* [TI]	2888
8	Claudicant* [TI]	112
9	Ankle Brachial Ind* [TI]	921
10	Critical limb* [TI]	1613
11	Amputation* [TI]	10430
12	Lower limb* [TI]	12289
13	Lower extremity* [TI]	9622
14	1 or 2 or 3 or 4 or 5	20891
15	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	40491
16	14 or 15	57338
17	Mortality [MH] OR Mortality [TW] OR Death* [TW] OR Survival [TW]	2379199
18	Cardiovascular Event [TW] OR Myocardial Infarction [TW]	234348
19	Stroke [MH] OR Stroke [TW] OR Cerebrovascular Event [TW] OR CVA [TW]	287473
20	17 or 18 or 19	2729424

Table 4.5: Adjusted variables in hazard ratios reported for all-cause mortality

AUTHOR	ADJUSTMENT FACTORS
AL-OMRAN, 2017	Age, procedure, risk factors (diabetes, hypertension), comorbidities (coronary artery disease)
BUDTZ-LILLY, 2015	Age, risk factors (BMI, diabetes, hypertension, tobacco use), comorbidities (creatinine, pulmonary disease, prior MI, prior CVA, prophylactic medication)
CEA SORIANO, 2017	Age, risk factors (BMI, smoking, hypertension, dyslipidaemia, DM), comorbidities (MI, IHD, CCF, AF, CVA, COPD, medication use), Townsend deprivation score
DUFFY, 2014	Age, race, smoking, comorbidities (CAD), risk factors (hypertension, statin use), operative factors (operation indication, pre-op ambulation, graft origin and recipient, conduit type), length of follow-up
FREISINGER, 2018	Propensity score matching: Age, risk factors (hypertension, smoking, obesity, dyslipidaemia), comorbidities (CAD, CCF, CKD, malignancies)
GROOTENBOER, 2011	Age, risk factors (hypertension, dyslipidaemia, diabetes, smoking), comorbidities (IHD, previous PCI/CABG, CCF, COPD, renal impairment), medication use (statin, beta blocker, aspirin)
HUSSAIN, 2016	Age, income level, comorbidities, medication use, use of healthcare services
JONES, 2013	Age, risk factors, comorbidities
MUSTAPHA, 2018	Age, race, geography, risk factors (hypertension, diabetes, coronary artery disease, chronic kidney disease, hyperlipidaemia, smoking), clinical presentation
SCHANZER, 2008	Age, race, institutional setting, risk factors, comorbidities, CLI, medication use, surgical
SIGVANT, 2017	Age, risk factors, comorbidities
TURLEY, 2017	Age, comorbidities (cancer, COPD, diabetes mellitus, dementia, heart failure, hypertension, ischemic heart disease, prior myocardial infarction, renal disease, stroke), location, type of intervention, clinical presentation
VAARTJES, 2009	Age, comorbidities

AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass graft; CCF, congestive cardiac failure; CKD, chronic kidney disease; CLI, critical limb ischaemia; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DM, diabetes mellitus; IHD, ischemic heart disease; MI, myocardial infarction; PCI, percutaneous coronary intervention

Table 4.6: Study inclusions and endpoints

AUTHOR	DATABASE AND STUDY INCLUSION	OUTCOME DATA
ABTAN, 2017	International Reduction of Atherothrombosis for Continued Health Registry Prospectively collected data from 7 geographical regions Inclusion: Age≥ 45, documented PAD with 1 or more of the following: active intermittent claudication with ankle-brachial index <0.9; history of intermittent claudication with previous peripheral vascular intervention including amputation No history of stroke/ transient ischemic attack	Primary outcome: MACE at 4 years MACE definition: composite of cardiovascular death, myocardial infarction and stroke
AL-OMRAN, 2003	Canadian Institute of Health Information and Ontario Health Insurance Plan Database recorded discharges from all acute care hospitals in Ontario, including day surgeries. Inclusion: Arterial bypass surgery or percutaneous transluminal angioplasty for peripheral arterial occlusive disease ICD-9 code primary diagnosis and treatment codes were based on the Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures.	Comparison of revascularisation procedures Primary outcome: Cumulative survival rate and amputation-free survival rate
BUDTZ-LILLY, 2015	National Danish Vascular Registry Database of all patients undergoing surgery for PAD in Danish hospitals. All operations were primary revascularisation procedures. All data were entered prospectively. Patients were stratified according to the PAD surgical procedure performed. Indications included stable claudication and critical limb ischaemia.	Gender comparison Primary outcome: First incidence of myocardial infarction, stroke or death, each as an individual endpoint MACE definition: myocardial infarction, stroke, or death
CEA SORIANO, 2017	United Kingdom observational cohort Database enrolment initiated via primary care physician. Requirement was for the patient to be known for at least 2 years, with at least 1 clinic visit during that time. Inclusion: Age 50-89 years and symptomatic PAD Automated database search using Read codes indicative of symptomatic PAD diagnosis and/or related surgical procedures.	Comparison between symptomatic PAD and a matched cohort without PAD Primary outcome: Incidence of MACE MACE definition: myocardial infarction, ischemic stroke or cardiovascular-related death
DUFFY, 2014	Vascular Study Group of New England Prospectively collected data following infrainguinal lower extremity bypass operation	Gender comparison Primary outcome: ambulatory status and living status at discharge and 1-year follow-up
FREISINGER, 2018	Public German health insurance database Inclusion: Index hospitalisation with ICD-10 codes 170.20-170.24 as primary diagnoses or secondary diagnosis combined with at least one of the following main diagnoses: diabetes with vascular complications, other peripheral vessel diseases, arterial embolism and thrombosis, or ulcers.	Gender comparison with propensity score matching Primary outcome: In-hospital and long-term complications following PAD-related hospitalisation

	Diagnostic, endovascular and surgical procedures were coded using German procedure classification	
GROOTENBOER, 2011	Prospectively collected data of all patients undergoing non-cardiac open vascular surgery at the Erasmus MC, Rotterdam, the Netherlands Participants that were included underwent non-cardiac vascular surgery, such as peripheral arterial occlusive disease	Gender comparison Primary outcome: Long-term all-cause mortality
HUSSAIN, 2016	Ontario administrative dataset Billing code algorithm and ICD-9/ ICD-10 codes for peripheral artery disease Inclusion: Age≥ 40, diagnosis of PAD within 3 years before a visit to Vascular Surgeon in Ontario	Gender comparison Primary outcome: MACE MACE definition: composite of death or hospital admission for stroke or myocardial infarction
JONES, 2013	US Centers for Medicare and Medicaid Services Medicare administrative claims for PAD-related hospitalisation. Inclusion: ICD-9-CM diagnosis code or procedure code for lower extremity peripheral artery disease.	Comparison between PAD cohort with lower extremity amputation and those without Primary outcome: All-cause mortality
MUSTAPHA, 2018	US Medicare administrative claims for critical limb ischaemia hospitalisations Inclusion: Critical limb ischaemia primary diagnosis (ICD-9 codes 440.22-440.24) or critical-limb ischaemia-related procedure code (endovascular revascularisation, surgical revascularisation, above or below ankle amputation)	Propensity score matching comparing endovascular revascularisation, surgical revascularisation and major amputation Primary outcome: Survival and major amputation through 4-year follow-up
SCHANZER, 2008	The Project of Ex-Vivo vein graft Engineering via Transfection III (PREVENT III) cohort Multicentre, randomised prospective trial testing the efficacy of edifoligide for prevention of graft failure Inclusion: Critical limb ischaemia undergoing lower extremity bypass grafting	Propensity score matching examining the effect of statins, beta-blockers and antiplatelet agents Primary outcome: MACE ≤30 days, vein graft patency and 1-year survival Definition of MACE: composite of myocardial infarction, stroke or death
SIGVANT, 2017	Swedish National Registry for Vascular Surgery Prospectively collected data for vascular procedures in Sweden Inclusion: Age> 50 years. Underwent lower limb revascularisation for chronic PAD	Examined effects of secondary preventive drug treatment Primary outcome: MACE MACE definition: nonfatal myocardial infarction, nonfatal ischemic stroke and cardiovascular death
TURLEY, 2017	US Centers for Medicare and Medicaid Services Medicare beneficiaries with a diagnosis of PAD identified by ICD-9-CM codes. Peripheral revascularisation procedures were identified using CPT codes. Inclusion: Age ≥ 65, undergoing lower extremity revascularisation procedure	Comparison of inpatient and outpatient clinical care settings Primary outcome: 30-day and 1-year rate of all-cause mortality, major lower extremity amputation, repeat revascularisation, and all-cause hospitalisation following peripheral vascular intervention

VAARTJES, 2009	National Hospital Discharge Registry and the Dutch Population Registry. Nationwide database of hospital admissions First hospital admission for PAD (defined by ICD-9 codes). Those with a previous admission for PAD were excluded	Gender comparison Primary outcome: Mortality

Table 4.7: Study quality analysis

STUDY CHARACTERISTIC	REFERENCE
Study design	
Administrative dataset	Al-Omran, Cea Soriano, Freisinger, Hussain, Jones, Mustapha, Turley, Vaartjes
Hospital or community cohort	Abtan, Budtz-Lilly, Duffy, Grootenboer, Sigvant
Randomised clinical trials	Schanzer
Gender comparison	Budtz-Lilly, Duffy, Freisinger, Grootenboer, Hussain, Vaartjes
Inclusion	
Procedure	
Arterial bypass surgery	Abtan, Al-Omran, Budtz-Lilly, Duffy, Freisinger, Grootenboer, Jones, Mustapha, Schanzer, Sigvant, Turley
Endovascular surgery	Abtan, Al-Omran, Budtz-Lilly, Freisinger, Jones, Mustapha, Sigvant, Turley
Amputation	Abtan, Budtz-Lilly, Jones, Mustapha
Non-procedural diagnosis	Abtan, Cea Soriano, Hussain, Vaartjes
Age-criteria	Abtan, Cea Soriano, Hussain, Sigvant, Turley
Follow-up point	
Admission	Al-Omran (Arterial bypass surgery), Freisinger, Vaartjes
Post-procedure	Al-Omran (Endovascular), Budtz-Lilly, Grootenboer, Jones, Mustapha, Sigvant, Turley
Discharge	Duffy
After randomisation/ enrolment	Abtan, Schanzer
Multiple starting points	Cea Soriano, Hussain
Follow-up duration	
12 months	Schanzer, Turley
1-4 years	Al-Omran, Duffy, Freisinger, Jones, Mustapha, Sigvant
≥ 4 years	Budtz-Lilly, Cea Soriano, Grootenboer, Hussain, Vaartjes

Table 4.8: Gender characteristics

CHARACTERISTIC	Higher Percentage in Women	No Difference Between Genders	Higher Percentage in Men
Comorbidities			
Hypertension	Freisinger, Budtz-Lilly, Duffy, Grootenboer		
Diabetes Mellitus		Hussain, Duffy, Grootenboer	Freisinger, Budtz-Lilly
Smoking			Freisinger, Budtz-Lilly, Duffy, Grootenboer
Obesity			Freisinger
CAD/ MI		Hussain	Freisinger, Budtz-Lilly, Duffy, Grootenboer
CVD		Hussain	Budtz-Lilly
CKD		Duffy, Grootenboer	Hussain
CHF	Freisinger	Duffy	Hussain
COPD/ Lung disease	Budtz-Lilly	Hussain, Duffy, Grootenboer	
Non- ambulatory	Duffy		
Clinical Presentation			
CLI	Freisinger, Duffy		
IC			Freisinger, Budtz-Lilly, Duffy
Medications			
Statin		Hussain, Budtz-Lilly, Grootenboer	Duffy
Antithrombotic	Budtz-Lilly	Duffy	Hussain
Antihypertensive	Hussain		
Procedures			
Any revascularisation		Freisinger	
Surgery			Freisinger
Endovascular	Freisinger		

Five studies included that performed a gender comparison. Vaartjes was not included as it performed an adjusted analysis. Abbreviations: CAD, coronary artery disease; CHF, chronic heart failure; CKD, chronic kidney disease; CLI, critical limb ischaemia; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; IC, intermittent claudication; MI, myocardial infarction

Table 4.9: Studies not included due to sample size (n = 100-1000)

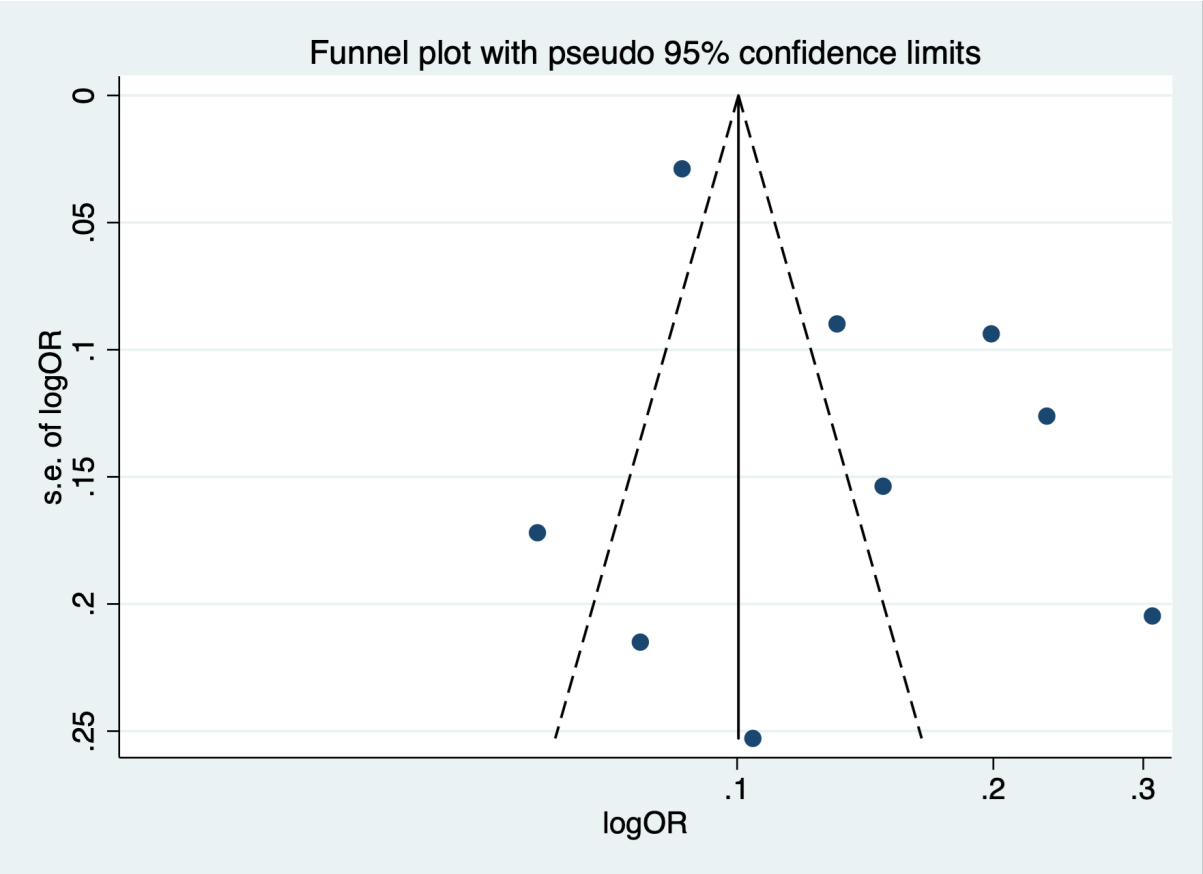
EXCLUDED STUDY	YEAR	TOTAL NUMBER	HR (M:F)	95% CI	95% CI	NOS
AQUARIUS	2009	184	2.30	0.60	8.60	8
BUNTE	2016	258	1.47	1.02	2.10	8
DREYER	2014	816	1.16	0.75	1.82	RCT
GARDNER	2008	434	1.97	0.96	4.07	9
GENOVESE	2016	411	0.67	0.46	0.96	9
HOWARD	2015	93 (ALI)	2.04	0.62	6.69	8
		202 (CLI)	0.78	0.38	1.63	
JEON-SLAUGHTER	2017	898	4.55	0.98	20.00	8
KLAPHAKE	2018	181	1.25	1.02	1.54	9
LEJAY	2015	584	0.67	0.49	0.93	8
OHMINE	2015	153	1.39	0.63	3.21	8
SENDA	2017	441	1.14	0.68	1.89	8
SHIRAKI	2014	459	0.89	0.60	1.44	8
SPRENGERS	2009	800	1.0	0.7	1.6	8
TAKAHARA	2010	278	1.38	0.78	2.41	9
TAKEJI	2018	643	1.17	0.89	1.58	8

Reported hazard ratios (HR) with 95% confidence interval of all-cause mortality in patients, with females as the reference group. Abbreviations: 95% CI, 95% confidence interval; ALI, acute limb ischaemia; CLI, critical limb ischaemia

Table 4.10: Studies removed due to duplicate dataset

REFERENCE	DATASET	STUDY CHARACTERISTICS AND REASON FOR EXCLUSION
FREISINGER, 2017 [213]	BARMER GEK	Assessed the impact of diabetes on critical limb ischaemia Freisinger performed propensity score matched gender analysis with BARMER GEK [185]
LUDERS, 2016[214]	BARMER GEK	Assessed the association of chronic kidney disease with morbidity and outcomes among patients with PAD
REINECKE, 2015[108]	BARMER GEK	Compared the outcomes of PAD based on clinical presentation
RICHTER, 2018 [215]	BARMER GEK	Assessed the impact of diabetes on treatment and outcomes of patients with PAD
WASMER, 2015[216]	BARMER GEK	Assessed the association of atrial fibrillation or flutter on outcomes of patients hospitalised for PAD
SI, 2018[217]	REACH	Assessed the prevalence and outcomes of undiagnosed peripheral among high-risk patients in Australia Abtan studied the largest PAD cohort from REACH [180]
WINKEL, 2010[218]	REACH	Assessed the prognosis of atrial fibrillation in patients with PAD
SUCKOW, 2015[219]	VSGNE	Assessed the impact of statin therapy after infrainguinal bypass surgery for critical limb ischaemia Duffy performed gender-specific comparison [184]
GOODNEY, 2010[220]	VSGNE	Assessed the factors associated with death 1 year after lower extremity bypass

Table 4.11: Funnel plot analysis



Egger's test for small-study effects: p=0.18

Overall summary estimate using trim and fill method: 1.13 (95% CI 1.10 to 1.16, p<0.001, I^2 88%)

CHAPTER 5: GENDER DIFFERENCES IN LONG-TERM OUTCOMES IN PAD – THE ACCELERATE TRIAL

ABSTRACT

Introduction: There are several recognised gender disparities in peripheral artery disease (PAD). Previous studies have found male gender to be associated with increased major adverse cardiovascular events (MACE) and mortality. However, there is a lack of high-quality comparative analyses to explain the observed differences in long-term outcomes.

Methods: ACCELERATE was a randomised trial of evacetrapib and placebo, which studied 626 females and 1,729 males with PAD. This analysis compared MACE and all-cause mortality rates according to gender.

Results: The rates of MACE in females and males were comparable (16.0% vs 17.4%, p=0.32, respectively). There was no significant difference in cardiovascular mortality (3.8% vs 5.8%, p=0.08), non-fatal myocardial infarction (6.1% vs 6.2%, p=0.98), non-fatal stroke (2.4% vs 2.8%, p=0.53), hospitalisation for unstable angina (2.2% vs 3.1%, p=0.11), and coronary revascularisation (8.2% vs 8.4%, p=0.52), in women compared with men. Females were significantly less likely to die from any cause than males (5.6% vs 9.2%, p=0.01). In the patients that achieved less optimal risk factor control, the incidence of all-cause mortality (4.7% vs 6.9%, p=0.36) was comparable for females and males, respectively. Female PAD patients that achieved more optimal risk factor control had significantly lower all-cause mortality than their male counterparts (4.0% vs 8.6%, p=0.004). Male gender was independently associated with all-cause mortality (adjusted hazard ratio [HR] 1.62, 95% CI, 1.11 to 2.38, p=0.01).

Conclusions: Male gender was associated with higher rates of mortality, and this was not attributable to gender differences in age, comorbidities, or non-fatal MACE. Women that achieved multiple risk factor control were significantly less likely to die than men, suggesting they might benefit more from intensive treatment. If the mechanisms contributing to this disparity were better understood, they could lead to better strategies in PAD treatment for both men and women.

5.1. Introduction

Peripheral artery disease (PAD) is associated with a high incidence of major adverse cardiovascular events (MACE) and mortality [24]. A scientific statement from the American Heart Association highlighted many gender disparities in PAD that weigh against women [140]. Females with PAD are less likely to experience intermittent claudication but are more afflicted with functional impairment and reduced quality of life [140-142]. The absence of typical symptoms and low clinical awareness of PAD could lead to more under-diagnosis and under-treatment in women [221]. Females are usually under-represented in clinical trials of medical and lifestyle therapies [140]. There could be differences in the utilisation of treatments, as some studies have found women to undergo lower extremity revascularisation less frequently than men [140, 222].

Despite these accepted gender disparities, chapter 4 showed that men had higher rates of MACE and mortality in long-term studies of symptomatic PAD. These differences in mortality were apparent across different clinical situations, although the divergence was potentially more significant with advanced disease requiring hospitalisation or a lower limb procedure. However, most of these studies did not focus on gender, and the potential for unmeasured confounders relating to risk factor control and treatment utilisation could not be excluded. It remains to be seen whether this discrepancy is due to clinical factors that negatively affect males, or if this is from females that have benefitted from treatment. Therefore, the mechanisms for the observed gender differences in MACE and mortality remain poorly understood.

ACCELERATE (Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at High Risk for Vascular Outcomes) was a randomised controlled trial of evacetrapib [148], which featured 626 females and 1,729 males with PAD.

In chapter 2, PAD patients in ACCELERATE experienced disproportionately high MACE rates, compared with coronary artery disease-only, even in the setting of multiple risk factor control [223]. In this chapter, we assessed the long-term outcomes in PAD patients according to gender, to determine whether previously described disparities were evident after adjusting for medical management and other covariates.

5.2. Methods

5.2.1. *Trial design and population*

This study was an exploratory analysis of a randomised controlled trial. ACCELERATE was a multicentre study, which compared the effects of evacetrapib and placebo in 12,092 statin-treated patients with atherosclerotic cardiovascular disease. Evacetrapib is a cholesteryl ester transfer protein inhibitor, which raises high-density lipoprotein cholesterol (HDL-C), reduces low-density lipoprotein cholesterol (LDL-C), and enhances cholesterol efflux capacity. Details of the study design, objectives, methods, and endpoints have previously been published [148]. The trial was sponsored by Eli Lilly and was coordinated by the Cleveland Clinic Coordinating Center for Clinical Research (C5Research) and Covance (Princeton, NJ).

For inclusion into ACCELERATE, participants had at least one of the following conditions: an acute coronary syndrome within the previous 30 to 365 days, atherosclerotic cerebrovascular disease, PAD, or diabetes with coronary artery disease. The PAD criterion was defined as current intermittent claudication or resting limb ischaemia and either an ankle-brachial index ≤0.90 or history of atherosclerotic limb ischaemia leading to previous non-coronary revascularisation or amputation. Some people with known PAD were not included on this basis, but an alternative diagnosis. All participants were required to take a maximally tolerated dose of statin and to meet specific lipid levels.

5.2.2. Study aims

ACCELERATE study outcomes have been previously detailed [148]. The primary outcome was a composite of MACE endpoints defined as either cardiovascular-related mortality, non-fatal myocardial infarction, non-fatal stroke, coronary revascularisation, or hospitalisation for unstable angina. There was no significant difference in the primary outcome between patients receiving evacetrapib and placebo, and the study was ceased after a mean follow-up of 28 months.

The aims of this analysis were to (1) compare the incidence of MACE and mortality in male and female patients with PAD, (2) evaluate these outcomes, according to multiple risk factor control, and (3) use logistic regression to identify clinical factors associated with MACE and mortality in PAD.

5.2.3. Stratification of optimal risk factor control

Risk factor control was evaluated at three months after randomisation. The targets were as followed: glycated haemoglobin (HbA1c) <7.0%, systolic blood pressure <130 mmHg, body mass index (BMI) ≤25, diastolic blood pressure <80 mmHg, LDL-C <70 mg/dL (1.80 mmol/L), triglycerides <150 mg/dL (1.70 mmol/L), high-sensitivity C-reactive protein (hs-CRP) <2.0 mg/L, and smoking abstinence. The patients were categorised as having “more optimal” control when 4 to 8 targets were met, and “less optimal” control for 0 to 3 risk factor targets achieved.

5.2.4. Statistical analysis

Baseline clinical characteristics of male and female patients were compared using the Wilcoxon test for continuous variables and chi-square test for categorical variables. The Cox proportional hazard regression model was used to assess for the effect of gender on mortality and MACE. The associations were reported as hazard ratios (HR) with a 95% confidence interval, where $p < 0.05$ was considered significant. Kaplan-Meier curves were created for the rate of the first occurrence of MACE and all-cause mortality in men and women. All analyses used STATA 15.1 (StataCorp, College Station, TX).

5.3. Results

5.3.1. Baseline characteristics

There was a total of 2,355 participants with PAD, inclusive of 626 (26.6%) females and 1,729 males. The baseline characteristics stratified by gender are outlined in Table 5.1. The groups were of similar age. Females had a higher mean body mass index (30.2 vs 29.4, p=0.001), and had less history of coronary artery disease (57.2% vs. 72.0%, p<0.001), acute coronary syndrome (27.6% vs 39.8%, p<0.001), coronary artery bypass graft surgery (33.4% vs 46.4%, p<0.001) and lower limb revascularisation (39.1% vs 46.3%, p=0.002), compared with males. There were less women taking statins (93.5% vs 96.3%, p=0.003) and ACE-inhibitor or ARB (71.7% vs 75.5%, p=0.004), than men.

Table 5.1: Baseline characteristics

Characteristic	Female (N = 626)	Male (N = 1,729)	p value
Age (years)	66.3 ± 9.3	66.5 ± 8.6	0.56
White race (N, %)	501 (80.0)	1,546 (89.4)	<0.001
Body mass index	30.2 ± 6.4	29.4 ± 5.0	0.001
PAD history (N, %)			
PAD inclusion criteria*	449 (71.7)	1,225 (70.9)	0.68
Ankle brachial index ≤0.9	376 (85.1)	994 (84.4)	0.73
Limb revascularisation	245 (39.1)	801 (46.3)	0.002
Amputation	25 (4.0)	91 (5.3)	0.73
Coronary artery disease history (N, %)	358 (57.2)	1,245 (72.0)	<0.001
Acute coronary syndrome	173 (27.6)	688 (39.8)	<0.001
PCI	224 (62.6)	770 (61.8)	0.80
CABG	120 (33.4)	578 (46.4)	<0.001
Cerebrovascular disease (N, %)	223 (35.6)	634 (36.7)	0.64
Current smoking (N, %)	155 (24.8)	452 (26.1)	0.50
Diabetes (N, %)	384 (61.3)	988 (57.1)	0.07
Baseline medication use (N, %)			
Statin	585 (93.5)	1,665 (96.3)	0.003
ACE inhibitor/ ARB	449 (71.7)	1,340 (77.5)	0.004
Aspirin	456 (72.8)	1,292 (74.7)	0.36
Diabetes medication	348 (55.6)	901 (52.1)	0.14
Antihypertensive	561 (89.6)	1,547 (89.5)	0.92

*Age and BMI expressed as mean ± standard deviation. *Participants that were included into ACCELERATE based on PAD eligibility criteria. Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin 2 receptor blocker; CABG, coronary artery bypass graft; PAD, peripheral artery disease; PCI, percutaneous coronary intervention*

5.3.2. Incidence of MACE and all-cause mortality

The rates of MACE in females and males were comparable (16.0% vs 17.4%, p=0.32, respectively) (Table 5.2 and Figure 5.1). There was a fewer number of cardiovascular-related deaths in females, although this was not significantly different (3.8% vs 5.8%, p=0.08). There were similar rates of non-fatal myocardial infarction (6.1% vs 6.2%, p=0.98), non-fatal stroke

(2.4% vs 2.8%, p=0.53), hospitalisation for unstable angina (2.2% vs 3.1%, p=0.11), and coronary revascularisation (8.2% vs 8.4%, p=0.52), in women compared with men. Females were significantly less likely to die from all-causes than males (5.6% vs 9.2%, p=0.01) (Figure 5.2). For patients that achieved less optimal risk factor control, the incidence of MACE (20.0% vs 16.5%, p=0.79) and all-cause mortality (4.7% vs 6.9%, p=0.36) were comparable for females and males, respectively (Table 5.3). For PAD patients achieving more optimal risk factor control, females had lower rates of all-cause mortality (4.0% vs 8.6%, p=0.03), while differences in MACE did not meet statistical significance (13.2% vs 17.4%, p=0.07).

Table 5.2: Incidence of events according to gender

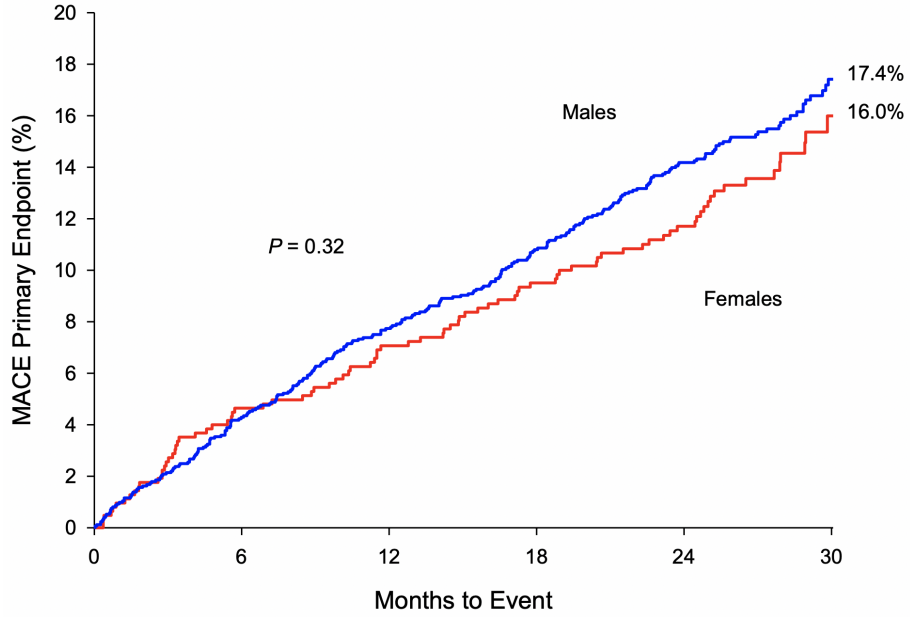
Events (N, %)	Female (N = 626)	Male (N = 1,729)	p value
MACE composite	87 (16.0)	268 (17.4)	0.32
Cardiovascular mortality	22 (3.8)	90 (5.8)	0.08
Non-fatal myocardial infarction	35 (6.1)	95 (6.2)	0.98
Non-fatal stroke	12 (2.4)	40 (2.8)	0.53
Hospitalisation for unstable angina	10 (2.2)	47 (3.1)	0.11
Coronary revascularisation	43 (8.2)	131 (8.4)	0.52
All-cause mortality	32 (5.6)	143 (9.2)	0.01

Table 5.3: Risk factor control and outcomes according to gender

Events, %	Female	Male	p value
MACE			
Less optimal control	20.0	16.5	0.79
More optimal control	13.2	17.4	0.07
All-cause mortality			
Less optimal control	4.7	6.9	0.36
More optimal control	4.0	8.6	0.004

Less optimal control defined as <4 of 8 risk factor targets achieved. More optimal control defined as ≥4 of 8 risk factor targets achieved.

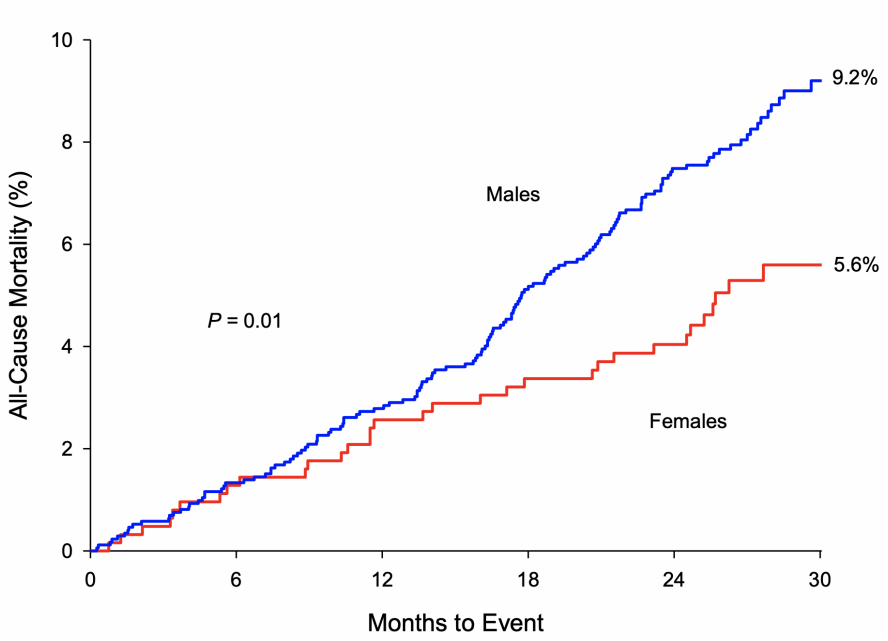
Figure 5.1: Kaplan-Meier survival curve for the first occurrence of MACE



Number at risk

Males	1,729	1,646	1,573	1,500	1,302	341
Females	626	593	573	555	480	122

Figure 5.2: Kaplan-Meier survival curve for all-cause mortality



Number at risk

Males	1,729	1,701	1,669	1,624	1,439	389
Females	626	616	606	600	529	148

5.3.3. Factors associated with MACE and all-cause mortality

Multivariate analysis found age, body mass index, lower limb amputation, limb revascularisation, cerebrovascular disease, coronary artery disease, acute coronary syndrome, diabetes mellitus and non-use of statins to be predictors of MACE (Table 5.4). Male gender was not associated with MACE (adjusted hazard ratio [HR], 1.00, 95% CI, 0.78 to 1.28, p=0.99). Logistic regression analysis identified older age, male gender, and history of lower limb revascularisation, cerebrovascular disease, and diabetes mellitus to be significantly associated with all-cause mortality (Table 5.5). Male gender was independently associated with all-cause mortality (adjusted HR 1.62, 95% CI, 1.11 to 2.38, p=0.01).

Table 5.4: Multivariate analysis of MACE

Characteristic	MACE		
	HR	95% CI	p value
Demographics			
Age (years)	1.02	1.01 – 1.03	0.001
Male gender	1.00	0.78 – 1.28	0.99
White	1.17	0.83 – 1.67	0.37
PAD history			
PAD inclusion criteria	0.97	0.76 – 1.23	0.79
ABI ≤0.9	0.74	0.54 – 1.01	0.06
Lower limb amputation	1.89	1.29 – 2.77	0.001
Limb revascularisation	1.37	1.11 – 1.70	0.003
Comorbidities			
Cerebrovascular disease	1.65	1.34 – 2.04	<0.001
Coronary artery disease	1.65	1.22 – 2.25	0.001
Acute coronary syndrome	1.34	1.06 – 1.69	0.01
Diabetes mellitus	1.48	1.17 – 1.87	0.001
Body mass index	1.02	1.00 – 1.04	0.03
Current smoker	1.03	0.79 – 1.33	0.84
Medication use			
Aspirin	1.06	0.83 – 1.36	0.65
Statin	0.63	0.42 – 0.95	0.03
ACE/ ARB	1.07	0.82 – 1.40	0.62
Diabetes medication	1.02	0.67 – 1.56	0.92
Antihypertensives	1.61	0.96 – 2.69	0.07

Abbreviations as per Table 5.1.

Table 5.5: Multivariate analysis of all-cause mortality

Characteristic	All-cause mortality		
	HR	95% CI	p value
Demographics			
Age (years)	1.04	1.02 – 1.06	<0.001
Male gender	1.62	1.11 – 2.38	0.01
White race	0.92	0.59 – 1.44	0.73
PAD history			
PAD inclusion criteria	1.23	0.90 – 1.78	0.17
ABI ≤0.9	0.83	0.51 – 1.35	0.46
Lower limb amputation	3.38	2.19 – 5.23	< 0.001
Limb revascularisation	1.32	0.98 – 1.79	0.07
Comorbidities and history			
Cerebrovascular disease	1.53	1.13 – 2.06	0.005
Coronary artery disease	1.25	0.87 – 1.77	0.23
PCI	0.74	0.53 – 1.04	0.09
Acute coronary syndrome	1.33	0.98 – 1.81	0.06
Diabetes mellitus	1.47	1.07 – 2.02	0.02
Body mass index	1.00	0.97 – 1.03	0.77
Current smoker	0.86	0.58 – 1.27	0.45
Medication use			
Aspirin	0.91	0.65 – 1.26	0.57
Statin	0.80	0.42 – 1.52	0.49
ACE-inhibitor/ ARB	0.86	0.60 – 1.23	0.42
Diabetes medication	1.08	0.58 – 1.99	0.82
Antihypertensives	1.32	0.71 – 2.46	0.38

Abbreviations as per Table 5.1.

5.4. Discussion

This study examined gender differences of a PAD cohort in a clinical trial setting. The incidence of MACE was comparable for men and women, and this was the predominant cause of death. Male PAD patients had considerably higher all-cause mortality than females, consistent with the findings of the meta-analysis in chapter 4. The gender difference in mortality was most evident for PAD patients that had more optimal risk factor control, which could be reflecting how women benefitted from intensive treatment. There was a disconnect between non-fatal MACE and all-cause mortality. In addition to the male gender, lower limb amputation appeared more predictive of all-cause mortality than MACE. This could be pointing to major adverse limb events, as the cause of gender differences in mortality, although these occurrences were not recorded in this study.

In chapter 2, PAD patients from ACCELERATE experienced higher MACE than coronary artery disease-only, even in the setting of multiple risk factor control [223]. There are many difficulties with reducing the risk of adverse events in these patients. Intermittent claudication and limb-threatening ischaemia correlate with considerable functional impairment and various medical comorbidities [18, 31, 204, 210, 224]. Lower extremity revascularisation carries a risk of major adverse limb events, including amputation, and acute limb ischaemia [27, 28, 225]. PAD patients are less likely to receive guideline-recommended therapies and optimal risk factor control, compared with coronary artery disease [10]. The theoretical incentive to treat PAD is higher, as these medications have potentially a dual benefit of reducing MACE and major adverse limb events [147]. Studies have found that the attitudes of clinicians and their patients are contributing to the under-treatment of PAD [13]. A higher medical complexity could be complicating clinical decisions to prescribe intensive treatments, such as antithrombotics, hypertension, diabetes, and dyslipidaemia. This problem underscores the importance of examining risk factor control and treatment utilisation in all PAD patients.

The disconnect between the rates of non-fatal MACE and all-cause mortality was inverse to the ODYSSEY trial. That study compared 18,924 patients with a recent acute coronary syndrome, which were randomised to alirocumab (proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitor) or placebo [226]. Non-fatal cardiovascular events were proportional to a higher rate of cardiovascular and non-cardiovascular mortality. Alirocumab was associated with a relative risk reduction in all-cause mortality (HR 0.85; 95% CI, 0.73 to 0.98, p=0.03), including fewer non-cardiovascular causes. Steg *et al.* suggested many explanations for the beneficial effects of alirocumab on non-cardiovascular deaths. Non-fatal MACE could be instrumental in the development of further disability, frailty, and susceptibility to non-cardiovascular illnesses [227]. The ODYSSEY trial investigated coronary artery disease patients, whereas this analysis was of PAD. Here, the link between non-fatal MACE and functional disability could be weaker, as these patients have overriding lower limb issues. Moreover, ACCELERATE was a shorter study and could be too narrow to observe a progression from non-fatal MACE to non-cardiovascular mortality.

Female PAD patients that achieved more optimal risk factor control had a lower incidence of all-cause mortality than their male counterparts. Given the separation between non-fatal MACE and all-cause mortality, risk factor control may have disproportionately reduced major adverse limb events in women. The interaction between conventional risk factors and PAD, according to gender, are not as well understood as with coronary artery disease. In general, smoking has a more substantial role in PAD, whereas hypertension and elevated LDL-C, correlate less, than with coronary artery disease [1, 16, 17]. Diabetes, HDL-C, and triglycerides have been associated with a higher risk of coronary artery disease in women, compared to men. Additionally, smoking and elevated hs-CRP appear to be more deleterious in female coronary artery disease patients than for males [177, 228, 229]. Diabetes has been more associated with intermittent claudication in women than in men [177]. Whether

risk factor control affects PAD differently in men and women needs clarification. While contemporary clinical trials have investigated the effects of medical treatment in preventing MALE, fewer women are usually enrolled [140]. This study raises the possibility that women with PAD benefit more from intensive risk factor control than men.

The Kaplan-Meier survival curves for all-cause mortality visually separated at fifteen months after randomisation and were widest apart at study end. In chapter 4, we proposed that the gender disparities in all-cause mortality could be more significant with advanced disease requiring hospitalisation or lower extremity revascularisation. The ACCELERATE study randomised patients to evacetrapib or placebo, based on a history of high-risk atherosclerotic conditions, which included PAD. In clinical trials of this nature, participants are usually stable for inclusion and mostly followed in an outpatient setting. The number of lower extremity revascularisation procedures were not documented, but this procedure is an essential contributor to morbidity and mortality. If there were gender differences in the utilisation of lower extremity revascularisation, as has been observed in some previous studies [140], this could explain the divergence in the Kaplan-Meier survival curves during follow-up. The clinical decisions surrounding lower extremity revascularisation are highly individualised, and operator dependent [19, 230]. Further research is needed to understand these decisions, as they relate to gender.

Some caveats should be noted. This study was an exploratory analysis of ACCELERATE, which investigated the efficacy of evacetrapib in high-risk cardiovascular conditions. Major adverse limb events and lower extremity revascularisation were not studied endpoints. These factors can have a profound impact on outcomes in PAD and are not necessarily related to MACE [231]. Defining the severity of lower extremity disease was not a primary focus, and we could not evaluate their role in the gender disparities. Psychosocial factors and functional status were also not assessed. However, the advantage of

ACCELERATE was the comprehensive information obtained regarding patient demographics and cardiovascular-related issues. These details were more extensive and more reliable than the administrative data in the studies that were reviewed in chapter 4. ACCELERATE examined participants that were eligible for inclusion into a cardiovascular outcome trial. This group would be more homogenous than people observed in hospital registry-based studies. Patients in ACCELERATE were less likely to be affected by unmeasured confounders concerning a PAD-related hospitalisation or procedure.

An enrolment bias limits clinical trials. In ACCELERATE, 27% of PAD patients were female, whereas this would be near parity if it reflected the disease prevalence [175]. An under-representation of women in clinical trials is typical for studies in this space [140]. There is an inherent rigidity that is associated with trial participation, which can limit the generalisability of findings to other clinical settings. These were well-managed PAD patients that had higher use of statins, antiplatelets, antihypertensives, and better risk factor control when compared with patients in other observational studies [10-12, 150]. Nevertheless, in chapter 4, we observed the association between male gender and increased rates of mortality in the non-trial setting. ACCELERATE provided an opportunity to evaluate the factors that could give rise to this disparity. The potential is there to review other cardiovascular outcome studies that feature PAD patients, to shed more light on this subject.

5.5. Conclusions

Male gender was associated with elevated all-cause mortality in PAD. Both men and women with this condition experienced high rates of MACE and mortality, and they require new approaches to management. Further research is needed to investigate if there are gender differences in long-term major adverse limb events and the responsible factors. The impact of

risk factor control on PAD outcomes in men and women need further evaluation. If this disparity was better understood, it could guide clinical practices and future healthcare initiatives.

CHAPTER 6: MAJOR ADVERSE LIMB EVENTS AND MORTALITY FOLLOWING LOWER EXTREMITY ENDOVASCULAR OR SURGICAL REVASCUALRISATION

ABSTRACT

Background: Major adverse limb events (MALE) cause permanent disability and contribute to the high rates of mortality in peripheral artery disease (PAD). Lower extremity revascularisation, either through endovascular or surgical means, can be complicated by MALE and other major adverse events, which require careful consideration. Persisting debate exists as to which approach has greater durability, and accordingly, lower risk of MALE in the longer term. Current evidence supporting the role of open vs endovascular revascularisation strategies are conflicting.

Methods: Patients undergoing lower extremity revascularisation with a primary diagnosis of PAD between 2008 and 2015 in the Australian Admitted Patient Collection and New Zealand National Minimum Dataset were examined. We evaluated long-term outcomes (up to eight years) of endovascular and surgical revascularisation, in both unmatched groups (surgery, n = 15,239; endovascular, n = 59,950) and with a propensity-score matched analysis (surgery, n = 14,560; endovascular, n = 14,560). The primary endpoint was MALE, defined as a composite of acute limb ischaemia, urgent surgery or endovascular reintervention, or major amputation. Secondary endpoints included mortality, elective surgical or endovascular reintervention, minor amputation, major bleeding, and all-cause acute hospitalisation. A multivariate logistic regression analysis identified factors that predicted a composite of MALE or mortality.

Results: In unmatched surgery and endovascular groups, the incidence of major adverse events was as followed: MALE (17.9% and 15.3%, p<0.0001), all-cause mortality (29.3% and 29.1%, p=0.89), MALE or all-cause mortality (40.4% and 38.3%, p<0.0001), major bleeding (9.6% and 8.2%, p<0.0001), all-cause acute hospitalisations (56.2% and 50.5%, p<0.0001), respectively. Predictors of MALE or mortality were age (years, hazard ratio [HR] 1.03, 95% CI, 1.02 to 1.03, p<0.0001), male gender (HR 1.08, 95% CI, 1.05 to 1.10, p<0.0001), critical

limb ischaemia (HR 1.53, 95% CI, 1.49 to 1.57, p<0.0001), vascular disease history (HR 1.14, 95% CI, 1.11 to 1.17, p<0.0001), prior PAD intervention (HR 1.16, 95% CI, 1.11 to 1.22, p<0.0001), lower limb amputation (HR 1.12, 95% CI, 1.04 to 1.21, p=0.005), and renal failure (HR 1.26, 95% CI, 1.21 to 1.31, p<0.0001). With a propensity-matched comparison, endovascular repair had a higher rate of all-cause mortality (HR 1.14, 95% CI 1.10 to 1.19, p<0.001), composite of MALE or all-cause mortality (HR 1.12, 95% CI, 1.07 to 1.16, p<0.001), and composite of other limb events (HR 1.12, 95 % CI, 1.09 to 1.15, p<0.001), but similar rates of MALE (HR 1.02, 95% CI, 0.96 to 1.07, p=0.58), major bleeding (HR 0.99, 95% CI, 0.92 to 1.07, p=0.84), all-cause acute rehospitalisation (HR 1.00, 95% CI 0.97 to 1.03, p=0.77), compared to surgery.

Conclusions: Enduring advantages of surgical revascularisation include lower all-cause mortality and endovascular reinterventions. The overall incidence of MALE or mortality was very high for both strategies, indicating patient comorbidities and potential limitation of treatment. Patients will benefit from multidisciplinary care and the ongoing advances in procedures and medications to alter the natural history of PAD in these advanced stages.

6.1. Introduction

A focal point of this thesis has been to compare PAD and coronary artery disease patients. Major adverse limb events (MALE) cause permanent disability and increased mortality. These occurrences are a factor that distinguishes this condition from coronary artery disease. The introductory chapter described how MALE and other major adverse events could complicate lower extremity revascularisation. When a patient with intermittent claudication is treated conservatively, the likelihood of MALE is considered low [25, 26]. However, despite its risks, peripheral artery revascularisation is sometimes offered to ameliorate pain and walking impairment. At the other end of the spectrum, in managing critical limb ischaemia (CLI), there is a reliance on revascularisation to improve wound healing and limb salvage [19]. The incidence of MALE and other major adverse events after lower extremity revascularisation have not been well characterised in a local population or with an extended follow-up period.

Traditionally, revascularisation was achieved with open surgical repair, where lower extremity atherosclerotic plaques are removed by endarterectomy or bypassed using an autogenous vein or prosthetic graft [232]. Endovascular repair, consisting of balloon angioplasty and stent insertion, has evolved with drug-coating and has rapidly gained dominance as the more commonly used approach to revascularisation [233].

The popularity of endovascular repair stems from the less-invasive nature of these procedures, shorter length of hospital stay, and a perceived reduction in perioperative complications compared to open surgery [234]. However, persisting debate exists as to whether surgical repair leads to more lasting revascularisation, and therefore is associated with less reintervention and a lower long-term risk of major adverse limb events (MALE) and mortality. Current evidence favouring either strategy is limited, with few randomised trials directly comparing endovascular or surgical repair [235]. Existing clinical trials have also been

restricted by small sample size, open-label, and non-comparative designs, limiting the strength of their conclusions [236]. So, despite the widespread use of revascularisation for PAD treatment, the optimal strategy for durable outcomes has not been determined.

In this study, we evaluated long-term (up to eight-year) outcomes post revascularisation using national data from Australia and New Zealand. We examined the incidence of MALE (composite of acute limb ischaemia, urgent surgical or endovascular reintervention, or major lower limb amputation), mortality, and other adverse events. This study aimed to: (1) evaluate the incidence of MALE and other major adverse events after lower extremity revascularisation, (2) identify patient factors that were predictive of MALE or mortality, and (3) compare major adverse events following endovascular and surgical repair using propensity-score matching.

6.2. Methods

6.2.1. Data source

We used hospitalisation data from the Admitted Patient Collection from each Australia State and Territory and the equivalent New Zealand National Minimum Dataset (Hospital Events). These datasets record patient encounters for all in-patient and day-only admissions from all public and most private sector hospitals and day procedure centres. For each encounter, procedural data are collected using a standard set of variables including patient characteristics, primary and secondary diagnoses, all procedures performed and the patient status at discharge. In both Australia and New Zealand, diagnoses are coded as per the International Classification of Diseases, 10th Revision-Australian Modification (ICD-10-AM) and all procedures are coded according to the Australian Classification of Health Interventions (ACHI). Prior studies of coding accuracy in the Australian setting have shown >85% accuracy for diagnoses and

procedure coding with cardiovascular diagnoses and procedures being particularly well coded [237].

In Australia, patient's hospitalisation encounters were linked to subsequent hospitalisation and each individual's registry of deaths. Linkages of all health records were performed using probabilistic matching techniques based on multiple patient identifiers by designated data-linkage units within each region. In New Zealand, hospital encounters are linked nationally using a unique National Health Index number, and all deaths are recorded in the National Health Index sociodemographic profile.

The Human Research Ethics Committees of the University of Adelaide and respective Australian states and territories provided ethical approval to undertake the study with a waiver of informed consent to use de-identified patient data. Data from New Zealand are obtained under a data user agreement with the New Zealand Ministry of Health.

6.2.2. Study population

Figure 6.1 summarises the process of patient selection. We included patients ≥ 18 years hospitalised with a primary diagnosis of PAD who had surgical or endovascular revascularisation during their admission. ICD-10-AM diagnoses and ACHI procedure codes were used to define the patient selection. For patients with multiple hospitalisations in the study period, the first hospitalisation was considered as the index encounter. We excluded other vascular conditions or procedures, such as aortic aneurysm, carotid and upper extremity disease, hybrid interventions (combined open surgery and endovascular intervention), embolectomy (without angioplasty), and patients that discharge against medical advice.

6.2.3. Study outcomes

The primary outcome was the incidence of MALE, which was defined as any of the following: a primary diagnosis of acute limb ischaemia, urgent endovascular reintervention or embolectomy, urgent surgical reintervention, or major amputation (at or above the ankle). Secondary outcomes were individual MALE endpoints, all-cause mortality, all-cause unplanned readmissions, other limb events, and major bleeding. Other limb events included other presentations to hospital with a primary diagnosis of PAD, elective admissions for lower extremity reintervention, and minor amputation (below the ankle).

6.2.4. Statistical analysis

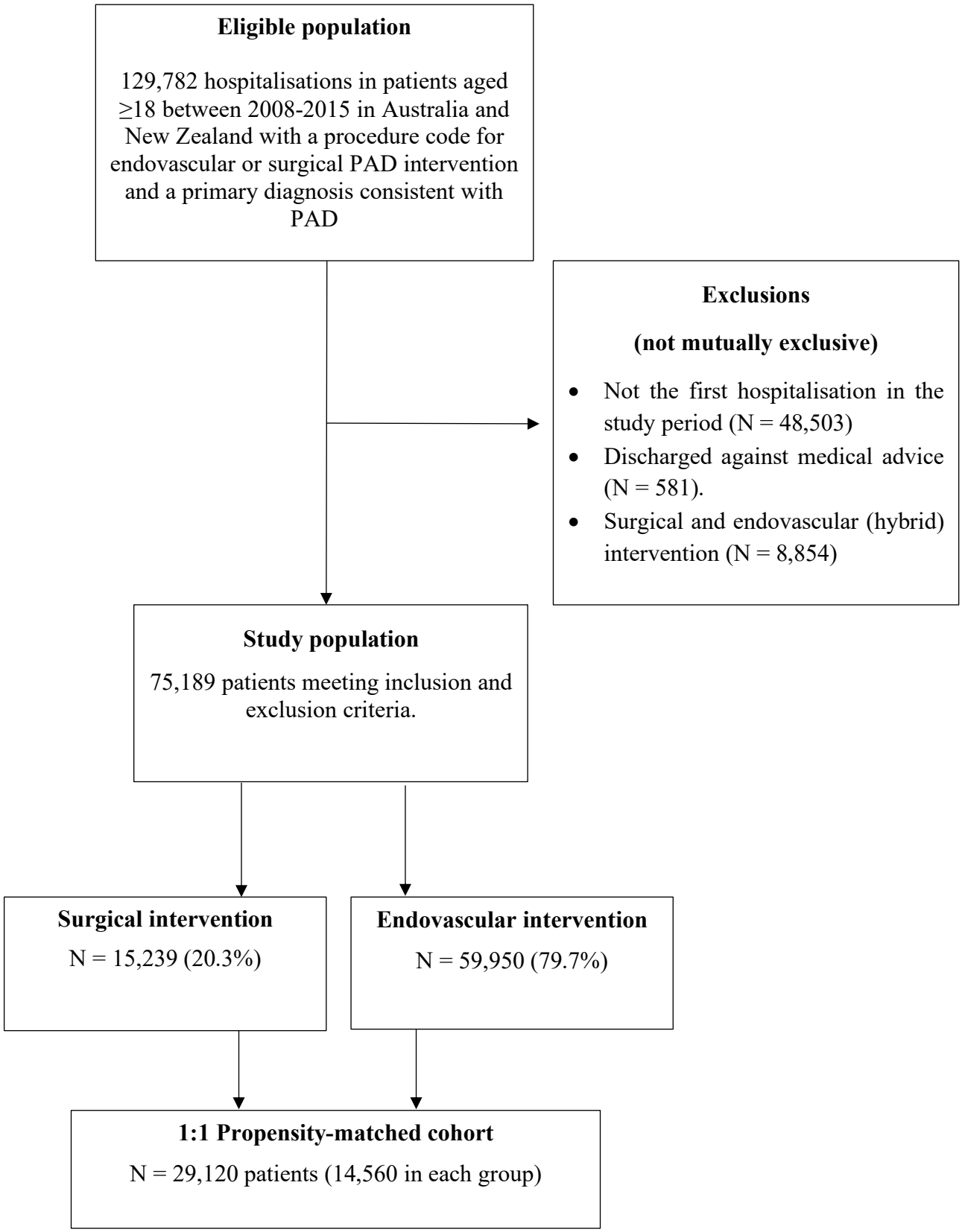
Data are summarised as frequencies and percentages for categorical variables. Continuous variables are presented as mean and standard deviation or median and interquartile range. . The chi-square and student's t-tests were used to compare endovascular and surgical intervention as appropriate.

We used propensity matching to account for differences in baseline characteristics arising from the non-random assignment of surgical or endovascular intervention. We then developed a propensity score, indicating the conditional probability that any individual patient would undergo endovascular intervention using a logistic regression model. Variables included patient age, gender, geographic region, vascular and limb history, cardiovascular history, and other comorbidities. Cardiac history and comorbidities were derived from the secondary diagnosis and procedure codes from the index hospitalisation and the principal and secondary codes from all hospitalisations in the preceding 12 months using the Condition Categories classification. Patients undergoing endovascular intervention were then matched 1:1 without replacement to patients that underwent surgery based on the propensity score a using a calliper

width of 0.01 to derive a propensity score-matched cohort. Further details of propensity-matching are outlined in the supplemental materials.

Unadjusted event-free survival curves in the propensity score-matched cohort were generated using Kaplan-Meier estimates and compared using the log-rank test. Adjusted survival curves were estimated using a Cox Proportional Hazards Model. All time-to-event outcomes were reported as HRs and 95% CI with patients treated with surgery as the reference group. The significance levels were 2-sided with a $p<0.05$, and the analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC).

Figure 6.1: Patient selection flow diagram



6.3. Results

6.3.1. Baseline characteristics of unmatched groups

75,189 patients were eligible, inclusive of 15,239 surgery and 59,950 endovascular cases. The baseline characteristics of unmatched groups are displayed in Table 6.1. Patients receiving surgery had lower mean age (70.8 vs 73.3, p<0.001), were more frequently men (73.5% vs 62.1%, p<0.001), a greater history of vascular disease (46.4% vs 22.4%, p<0.001), prior vascular intervention (6.5% vs 5.2%, p<0.001), and lesser prior lower limb amputation (4.6% vs 5.0%, p=0.05), compared to the endovascular group, respectively. Surgery was more frequently performed in an elective setting (78.5% vs 76.8%, p<0.001), and less commonly in a private hospital (29.3% vs 40.8%, p<0.001). There were significant differences across various cardiovascular and non-cardiovascular comorbidities. Surgical group had less history of acute coronary syndrome (5.1% vs 4.7%, p=0.004), congestive heart failure (7.4% vs 8.3%, p<0.001), diabetes (27.1% vs 30.8%, p<0.001), renal failure (8.3% vs 11.0%, p<0.001), compared to endovascular patients.

Table 6.1: Baseline characteristics of unmatched groups

Baseline characteristics	Overall		Surgical		Endovascular		p value
	N = 75,189		N = 15,239		N = 59,950		
	N	%	N	%	N	%	
Demographics							
Age (mean ± SD), yrs.	72.8 ± 11.7		70.8 ± 11.6		73.3 ± 11.6		<0.001
Age group							
18-54	5,452	7.3	1,339	8.8	4,113	6.9	<0.001
55-64	12,238	16.3	2,888	19.0	9,350	15.6	
65-74	21,925	29.2	4,901	32.2	17,024	28.4	
75-84	23,794	31.7	4,547	29.8	19,247	32.1	
≥85	11,780	15.7	1,564	10.3	10,216	17.0	
Male	48,456	64.5	11,206	73.5	37,250	62.1	<0.001
Presenting characteristics							
Elective	58,002	77.1	11,959	78.5	46,043	76.8	<0.001
CLI	21,856	29.1	4,394	28.8	17,462	29.1	0.48
Private hospital	28,947	38.5	4,465	29.3	24,482	40.8	<0.001
Presenting region							
NSW/ACT	23,923	31.8	3,437	22.6	20,486	34.2	<0.001
VIC	19,103	25.4	3,849	25.3	15,254	25.4	
QLD	10,331	13.7	3,319	21.8	7,012	11.7	
SA/NT	3,287	4.4	998	6.6	2,289	3.8	
TAS	694	0.9	145	1.0	549	0.9	
WA	8,621	11.5	829	5.4	7,792	13.0	
NZ	9,230	12.3	2,662	17.5	6,568	11.0	
Vascular and limb history							
Prior vascular disease	20,511	27.3	7,077	46.4	13,434	22.4	<0.001
Prior vascular intervention	4,107	5.5	987	6.5	3,120	5.2	<0.001
Prior limb amputation	3,671	4.9	698	4.6	2,973	5.0	0.05
Cardiovascular history							
Prior coronary angiogram	4,914	6.5	1,089	7.2	3,825	6.4	0.001
Prior PCI	1,777	2.4	309	2.0	1,468	2.5	0.002
Prior CABG	928	1.2	224	1.5	704	1.2	0.003
Acute coronary syndrome	3,837	5.1	708	4.7	3,129	5.2	0.004
Ischaemic heart disease	7,738	10.3	1,801	11.8	5,937	9.9	<0.001
Hypertension	23,290	31.0	5,215	34.2	18,075	30.2	<0.001
Congestive heart failure	6,096	8.1	1,129	7.4	4,967	8.3	<0.001
Valvular and rheumatic heart disease	1,687	2.2	398	2.6	1,289	2.2	<0.001
Arrythmia or conduction disorder	6,357	8.5	1,149	7.5	5,208	8.7	<0.001
Cerebrovascular diseases	2,384	3.2	504	3.3	1,880	3.1	0.28
Other comorbidities							
Diabetes	22,592	30.1	4,125	27.1	18,467	30.8	<0.001
Advanced or metastatic cancer	1,336	1.8	272	1.8	1,064	1.8	0.93
Other cancers and tumors	5,230	7.0	1020	6.7	4,210	7.0	0.15
Chronic lung disease	3,294	4.4	904	5.9	2,390	4.0	<0.001

Table 6.1. Continued

Baseline characteristics	Overall		Surgical		Endovascular		p value
	N = 75,189		N = 15,239		N = 59,950		
	N	%	N	%	N	%	
Other comorbidities							
Renal failure	7,874	10.5	1,267	8.3	6,607	11.0	<0.001
Pneumonia	3,297	4.4	747	4.9	2,550	4.3	<0.001
Haematological disorders	9,697	12.9	2,820	18.5	6,877	11.5	<0.001
Chronic liver disease	325	0.4	75	0.5	250	0.4	0.21
Dementia	1,825	2.4	302	2.0	1,523	2.5	<0.001
Psychiatric disorders	1,862	2.5	473	3.1	1,389	2.3	<0.001
Paralysis or functional disability	5,255	7.0	992	6.5	4,263	7.1	0.009
Parkinson and Huntington's disease	199	0.3	36	0.2	163	0.3	0.44
Seizure	343	0.5	68	0.5	275	0.5	0.84
Malnutrition	2,839	3.8	644	4.2	2,195	3.7	0.001
Other significant endocrine and metabolic disorder	1,695	2.3	381	2.5	1,314	2.2	0.02
Disorder of fluid and electrolytes	6,207	8.3	1,100	7.2	5,107	8.5	<0.001
HIV	76	0.1	20	0.1	56	0.1	0.19
Other significant endocrine/ metabolic disorder	8,919	11.9	2,211	14.5	6,708	11.2	<0.001
Inflammatory bowel disease	115	0.2	26	0.2	89	0.2	0.53
Bone, joint or muscle infection/ necrosis	2,728	3.6	439	2.9	2,289	3.8	<0.001
RA or inflammatory CTD	813	1.1	137	0.9	676	1.1	0.02
Spinal disorder	1,022	1.4	183	1.2	839	1.4	0.06
Hip or knee osteoarthritis	921	1.2	151	1.0	770	1.3	0.003
Artificial openings for feeding or elimination	439	0.6	103	0.7	336	0.6	0.10

Statistical comparison between unmatched surgical (n = 15,239) and endovascular (n = 59,950) groups. Age is expressed in mean ± standard deviation, years. Abbreviations: CABG, coronary artery bypass grafting; CLI, critical limb ischaemia; CTD, connective tissue disease; HIV, human immunodeficiency virus; PCI, percutaneous coronary intervention; RA, rheumatoid arthritis

6.3.2. Major adverse events in unmatched groups

During the period of observation following lower extremity revascularisation, the incidence of major adverse events for all patients (n = 75,189) was as follows: MALE (15.8%), all-cause mortality (29.1%), MALE or all-cause mortality (38.7%), other limb events (36.5%), major bleeding (8.5%), all-cause acute hospitalisation (51.6%) (see Table 6.2). In unmatched surgery (n = 15,239) and endovascular (n = 59,950) groups, the incidence of major adverse events was as follows: MALE (17.9% and 15.3%, p<0.0001), all-cause mortality (29.3% and 29.1%, p=0.89), MALE or all-cause mortality (40.4% and 38.3%, p<0.0001), major bleeding (9.6% and 8.2%, p<0.0001), all-cause acute hospitalisations (56.2% and 50.5%, p<0.0001), respectively.

6.3.3. Factors predictive of major adverse limb events or mortality

The predictors of a composite of MALE or mortality were identified using logistic regression model (Table 6.3). Significant factors included age (years, HR 1.03, 95% CI, 1.02 to 1.03, p<0.0001), male gender (HR 1.08, 95% CI, 1.05 to 1.10, p<0.0001), CLI (HR 1.53, 95% CI, 1.49 to 1.57, p<0.0001), vascular disease history (HR 1.14, 95% CI, 1.11 to 1.17, p<0.0001), prior PAD intervention (HR 1.16, 95% CI, 1.11 to 1.22, p<0.0001), prior lower limb amputation (HR 1.12, 95% CI, 1.04 to 1.21, p=0.005), acute coronary syndrome (HR 1.12, 95% CI, 1.06 to 1.19, p<0.0001), diabetes (HR 1.04, 95% CI, 1.01 to 1.07, p=0.01), renal failure (HR 1.26, 95% CI, 1.21 to 1.31, p<0.0001), advanced or metastatic cancer (HR 2.11, 95% CI 1.98 to 2.26, p<0.0001), and dementia (HR 1.38, 95% CI, 1.31 to 1.46, p<0.0001). Some cardiovascular history appeared protective, including cerebrovascular disease (HR 0.91, 95% CI 0.86 to 0.97, p=0.005), prior coronary angiogram (HR 0.70, 95% CI, 0.65 to 0.76,

p<0.0001), prior percutaneous coronary intervention (HR 0.89, 95% CI, 0.81 to 0.98, p=0.02), and prior coronary artery bypass graft operation (HR 0.73, 95% CI, 0.65 to 0.82, p<0.0001).

Table 6.2: Major adverse events in unmatched groups

Outcomes	Overall cohort (N = 75,189)	Surgical (N = 15,239)	Endovascular (N = 59,950)	p value
Primary endpoint				
MALE	11,900 (15.8%)	2,728 (17.9%)	9,172 (15.3%)	<0.0001
Secondary endpoints				
All-cause mortality	21,902 (29.1%)	4,457 (29.3%)	17,445 (29.1%)	0.89
All-cause mortality or MALE	29,116 (38.7%)	6,156 (40.4%)	22,960 (38.3%)	<0.0001
Major bleeding	6,366 (8.5%)	1,458 (9.6%)	4,908 (8.2%)	<0.0001
All-cause acute rehospitalisations	38,818 (51.6%)	8,570 (56.2%)	30,248 (50.5%)	<0.0001
MALE subcategories				
- Urgent surgical reintervention	2,402 (3.2%)	829 (5.4%)	1,573 (2.6%)	<0.0001
-Urgent endovascular reintervention	6,098 (8.1%)	1,201 (7.9%)	4,897 (8.2%)	0.26
-Major amputation	4,070 (5.4%)	1,049 (6.9%)	3,021 (5.0%)	<0.0001
-Thrombolysis	1,338 (1.8%)	295 (1.9%)	1,043 (1.7%)	0.25
-Arterial Emboli/Thrombus	3,972 (5.3%)	1,122 (7.4%)	2,850 (4.8%)	<0.0001
Other limb events	27,469 (36.5%)	4,882 (32.0%)	22,587 (37.7%)	<0.0001
- Elective surgical reintervention	7,827 (10.4%)	2,432 (16.0%)	5,395 (9.0%)	<0.0001
- Elective endovascular reintervention	21,310 (28.3%)	3,099 (20.3%)	18,211 (30.4%)	<0.0001
- Minor amputation	5,671 (7.5%)	969 (6.4%)	4,702 (7.8%)	<0.0001

Statistical comparison between unmatched surgical (n = 15,239) and endovascular (n = 59,950) groups.

Table 6.3: Multivariate analysis of major adverse limb events or mortality in all unmatched patients

Variable	HR	Lower 95% CL	Upper 95% CL	p value
Demographics				
Age (years)	1.03	1.02	1.03	<0.0001
Male gender	1.08	1.05	1.10	<0.0001
Presenting characteristics				
CLI	1.53	1.49	1.57	<0.0001
Elective procedure	0.60	0.59	0.62	<0.0001
Private hospital	0.89	0.86	0.91	<0.0001
Presenting region				
NSW/ACT	1.07	1.03	1.12	<0.0001
NZ	1.18	1.13	1.24	
QLD	1.01	0.96	1.06	
SA/NT	1.11	1.04	1.18	
TAS	1.24	1.11	1.40	
VIC	0.92	0.88	0.96	
Vascular and limb history				
Vascular disease	1.14	1.11	1.17	<0.0001
Prior PAD intervention	1.16	1.11	1.22	<0.0001
Lower limb amputation	1.12	1.04	1.21	0.005
Cardiovascular history				
Prior coronary angiogram	0.70	0.65	0.76	<0.0001
Prior PCI	0.89	0.81	0.98	0.02
Prior CABG	0.73	0.65	0.82	<0.0001
Acute coronary syndrome	1.12	1.06	1.19	<0.0001
Ischaemic heart disease	1.17	1.11	1.22	<0.0001
Hypertension	1.23	1.19	1.26	<0.0001
Arrythmia or conduction disorder	1.06	1.02	1.10	0.003
Cerebrovascular diseases	0.91	0.86	0.97	0.005
Other Comorbidities				
Diabetes	1.04	1.01	1.07	0.01
Advanced or metastatic Cancer	2.11	1.98	2.26	<0.0001
Chronic lung disease	1.38	1.31	1.44	<0.0001
Pneumonia	1.19	1.13	1.25	<0.0001
Renal failure	1.26	1.21	1.31	<0.0001
Hematological disorders	1.14	1.10	1.18	<0.0001
Chronic liver disease	1.74	1.53	1.99	<0.0001
Dementia	1.38	1.31	1.46	<0.0001
Psychiatric Disorders	1.18	1.11	1.25	<0.0001
Paralysis or functional disability	1.14	1.06	1.22	0.0003
Seizures	1.21	1.06	1.40	0.007
Other significant endocrine and metabolic disorders	1.10	1.03	1.17	0.006
Disorders of fluid and electrolytes	0.93	0.90	0.97	0.001
HIV	1.66	1.16	2.37	0.006
Other endocrine/metabolic/nutritional disorders	1.17	1.13	1.21	<0.0001

Table 6.3. Continued

Variable	HR	Lower 95% CL	Upper 95% CL	p value
Inflammatory bowel disease	1.35	1.04	1.75	0.02
Bone, joint, or muscle infection/ necrosis	0.90	0.85	0.95	<0.0001
RA or inflammatory CTD	1.48	1.35	1.61	<0.0001
Spinal disorder	0.88	0.81	0.97	0.01
Organ transplant status	1.19	1.14	1.25	<0.0001
Incontinence, UTI and other urinary tract disorders	1.16	1.12	1.21	<0.0001
Chronic ulcers	1.17	1.13	1.22	<0.0001
Artificial openings for feeding or elimination	1.28	1.13	1.44	<0.0001

CABG, coronary artery bypass graft; CL, confidence limit; CTD, connective tissue disorder; HIV, human immunodeficiency virus; PCI, percutaneous coronary intervention; RA, rheumatoid arthritis; UTI, urinary tract infection

6.3.4. Propensity-matched comparisons of surgery and endovascular revascularisation outcomes

A defined comparison was made between patients undergoing endovascular intervention (n = 14,560) and surgical intervention (n = 14,560). When comparing the endovascular group to open surgery there were similar rates of MALE (HR 1.02, 95% CI, 0.96 to 1.07, p=0.58), major bleeding (HR 0.99, 95% CI, 0.92 to 1.07, p=0.84) and all-cause acute rehospitalisations (HR 1.00, 95% CI 0.97 to 1.03, p=0.77) (see Table 6.4). The endovascular group had a higher rate of all-cause mortality (HR 1.14, 95% CI 1.10 to 1.19, p<0.001), a composite of MALE or all-cause mortality (HR 1.12, 95% CI, 1.07 to 1.16, p<0.001), and a composite of other limb events (HR 1.12, 95 % CI, 1.09 to 1.15, p<0.001). Figure 6.2 and Figure 6.3 are Kaplan-Meier curves for the first occurrence of MALE, and the composite of MALE and mortality, according to revascularisation strategy. These curves illustrate the similarities in the rates of MALE and the lower likelihood of MALE or mortality for the surgery group.

Of the MALE subcategories, endovascular patients were less likely to require urgent surgical reintervention (HR 0.70, 95% CI, 0.63 to 0.78, p<0.001), or experience arterial embolus/ thrombus (HR 0.83, 95% CI, 0.76 to 0.91, p<0.001), but at the expense of higher urgent endovascular reintervention (HR 1.18, 95 % CI, 1.09 to 1.28, p<0.001). Examining other limb events that were not categorised as MALE, the endovascular patients had a higher elective endovascular intervention (HR 1.49, 95% CI, 1.42 to 1.56, p<0.001), and minor amputation (HR 1.35, 95% CI, 1.24 to 1.47, p<0.001), but fewer elective surgical reintervention (HR 0.65, 95% CI, 0.60 to 0.69, p<0.001).

Table 6.4: Major adverse events in propensity-matched groups

Outcomes	Overall cohort (N = 29,120)	Surgical (N = 14,560)	Endovascular (N = 14,560)	Hazard ratio (95% CI)	p value
Primary endpoint					
MALE	5,124 (17.6%)	2,607 (17.9%)	2,517 (17.3%)	1.02 (0.96 – 1.07)	0.58
Secondary endpoints					
All-cause mortality	8,692 (29.9%)	4,269 (29.3%)	4,423 (30.4%)	1.14 (1.10 – 1.19)	<0.001
MALE or all-cause mortality	11,826 (40.6%)	5,887 (40.4%)	5,939 (40.8%)	1.12 (1.07 – 1.16)	<0.001
Major bleeding	2,680 (9.2%)	1,389 (9.5%)	1,291 (8.9%)	0.99 (0.92 – 1.07)	0.84
All-cause acute rehospitalisations	15,967 (54.8%)	8,173 (56.1%)	7,794 (53.5%)	1.00 (0.97 – 1.03)	0.77
MALE subcategories					
- Urgent surgical reintervention	1,318 (4.5%)	789 (5.4%)	529 (3.6%)	0.70 (0.63 – 0.78)	<0.001
-Urgent endovascular reintervention	2,414 (8.3%)	1,145 (7.9%)	1,269 (8.7%)	1.18 (1.09 – 1.28)	<0.001
-Major amputation	1,966 (6.8%)	1,004 (6.9%)	962 (6.6%)	1.01 (0.92 – 1.10)	0.91
-Thrombolysis	558 (1.9%)	282 (1.9%)	276 (1.9%)	1.03 (0.87 – 1.22)	0.71
-Arterial Emboli/Thrombus	1,920 (6.6%)	1,070 (7.4%)	850 (5.8%)	0.83 (0.76 – 0.91)	<0.001
Other limb events	21,475 (73.8%)	10,589 (72.7%)	10,886 (74.8%)	1.12 (1.09 – 1.15)	<0.001
- Elective surgical reintervention	3,818 (13.1%)	2,340 (16.1%)	1,478 (10.2%)	0.65 (0.60 – 0.69)	<0.001
- Elective endovascular reintervention	6,949 (23.9%)	2,980 (20.5%)	3,969 (27.3%)	1.49 (1.42 – 1.56)	<0.001
- Minor amputation	2,133 (7.3%)	933 (6.4%)	1,200 (8.2%)	1.35 (1.24 – 1.47)	<0.001
-PAD-related readmission not meeting MALE criteria	13,078 (44.9%)	6,689 (45.9%)	6,389 (43.9%)	1.05 (0.15 – 7.43)	0.96

Hazard ratio expressed with surgical intervention as the reference group.

Figure 6.2: Kaplan-Meier survival curve for MALE according to revascularisation type

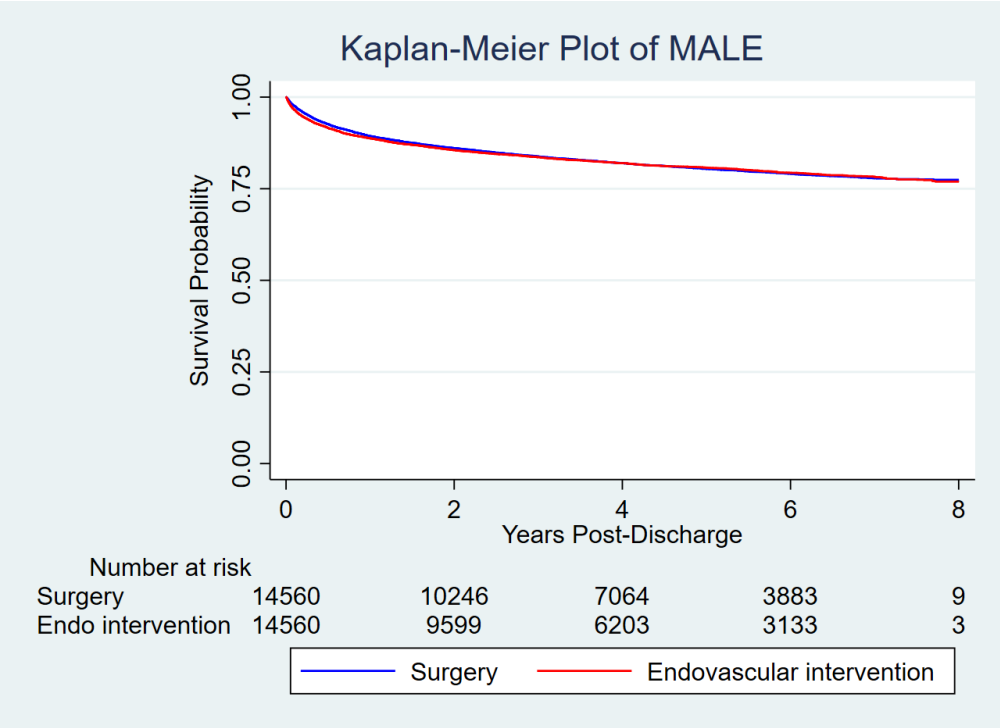
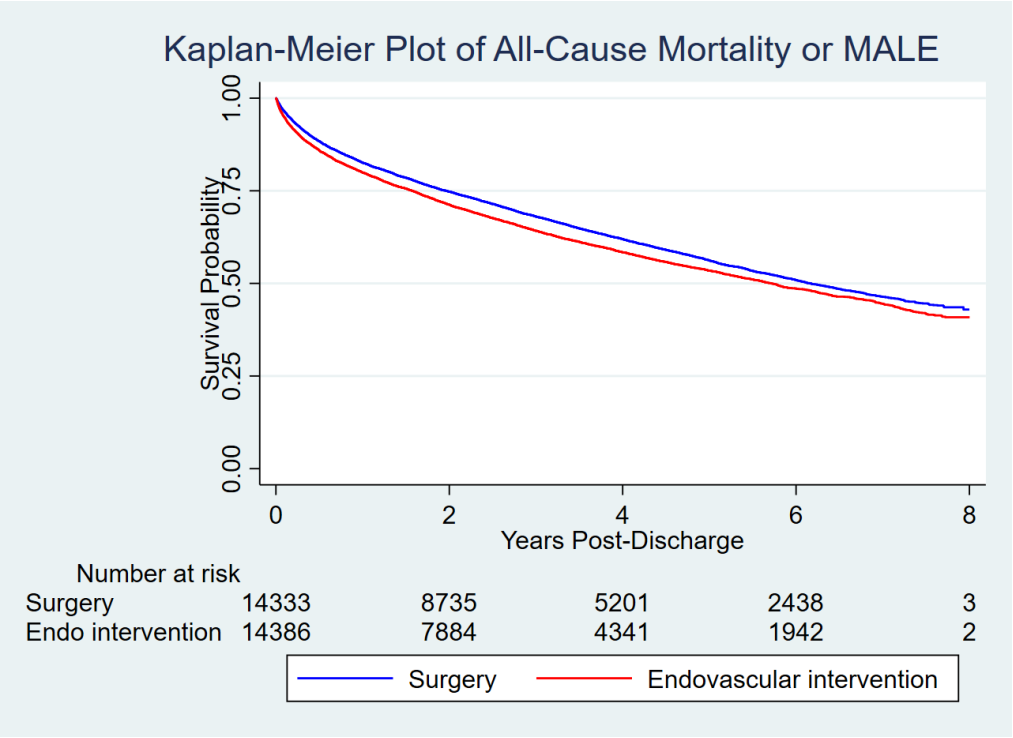


Figure 6.3: Kaplan-Meier survival curve for MALE or all-cause mortality according to revascularisation type



6.4. Discussion

This study evaluated the long-term outcomes of lower extremity revascularisation in an Australia and New Zealand population. After propensity-matching, the patients undergoing endovascular repair had a 14% higher likelihood of all-cause mortality, 12% higher MALE or all-cause mortality, 35% higher minor amputation, and 49% greater elective endovascular reintervention, compared to surgery. These were some enduring advantages for open surgery, which has become less favoured as it is more invasive. There were no significant differences in MALE, major bleeding, or all-cause acute rehospitalisation. The overall rates of MALE were 15.8%, all-cause mortality was 29.1%, and the composite of MALE or all-cause mortality was 38.7% during an extended follow-up period, suggesting new strategies are required. There were

several associations between medical comorbidities and MALE or mortality, indicating the complex multidisciplinary needs of these PAD patients.

Few randomised studies have compared endovascular and surgical revascularisation outcomes. The BASIL trial featured 452 patients presenting with CLI randomised to initial bypass surgery or balloon angioplasty. No significant differences in amputation-free survival were apparent during the first two years, although beyond that time, open surgery was associated with higher amputation-free survival [235, 238]. Our findings were consistent with the BASIL trial's long-term outcomes, as here the matched surgery patients were at lower long-term risk of mortality, as well as major and minor amputation. The BASIL trial had caveats that would limit generalisability to current practice. The study investigated a modest number of patients and only CLI presentations. Participant recruitment began twenty years ago, in an era before modern endovascular techniques, such as stenting. A high proportion (25%) of surgical patients received a prosthetic graft, which is less durable than the saphenous vein graft [19, 232]. In our cohort, encounters from 2008 onwards were chosen to reflect current vascular practice, thus incorporating more advanced endovascular interventions and progress in surgical planning. The endovascular approach was preferred, as evidenced by an approximate 4:1 ratio of endovascular to surgery cases in the unmatched groups, consistent with other recent observational studies [239, 240]. It can also be argued that the results of earlier studies have become less applicable, with the evolution of medical therapy, public health messages regarding smoking, clinical guidelines, and the familiarity that specialists have with newer procedures [10, 28, 87, 241]. These trends necessitate a comparative analysis in a more contemporary setting than with the BASIL study.

Our findings expand insights into PAD beyond the United States and other well-researched populations. The outcomes of lower extremity revascularisation are operator dependent and can differ across specialists [28, 242]. In Australia and New Zealand, vascular

surgeons and interventional radiologists primarily perform these procedures. The rates of MALE and mortality varied significantly between regions, which again, shows the value in studying multiple geographies. Also, PAD revascularisation performed in the private hospital setting appeared to have more favourable outcomes, compared to public hospitals. These findings could relate to differences in patient selection, operator experience, medical treatment and follow-up. Postprocedural surveillance is a potential driver of reintervention, and this might differ across healthcare systems. The current consensus is that patients should undergo serial imaging to evaluate vessel patency after lower extremity revascularisation [243]. The rationale for postprocedural surveillance is to detect arterial restenosis early, as this could be treated electively and with a less complicated procedure, than if this were to advance. The efficacy of these programs has not been demonstrated in a randomised clinical trial, and it is unclear how these influence the rates of MALE and other limb events [244].

Amputation-free survival is a common primary endpoint for studies of lower extremity revascularisation. We examined a broad MALE composite, which has been previously described [245]. Major amputation, acute limb ischaemia, and urgent reintervention are clinical endpoints that are likely indicative of an unsuccessful procedure. The introductory chapter highlighted the dangers of MALE and the importance of prevention. Modern clinical trials of medical therapies are increasingly incorporating MALE as an endpoint [31, 93, 246, 247]. With PAD being integrated with other areas of cardiovascular medicine, the examination of MALE consistently across the literature would be prudent.

Endovascular revascularisation is often preferred in sicker patients considered high risk for open surgery [19]. In this study, the unmatched surgery group were younger, and more likely elective, compared with the endovascular group. They had less history of acute coronary syndrome, congestive heart failure, diabetes, and renal failure, however other cardiorespiratory comorbidities were overrepresented. A traditional school of thought is that open surgery

achieves superior long-term arterial patency than endovascular repair when performed in less complicated patients [232]. Of the limb outcomes assessed, elective endovascular reintervention was the most frequent occurrence, affecting 20% of surgery, and 30% of the endovascular unmatched groups. This finding supports the idea that surgery can achieve better long-term outcomes for some patients. Notwithstanding, the exceptionally high rates of mortality would need to be factored when adopting this more invasive approach.

Most of the lower extremity revascularisations were performed in an elective and non-CLI setting. This raises questions as to the clinical scope in deferring these procedures and adopting a conservative approach. In prior observational studies, conservative management of intermittent claudication has corresponded with a low likelihood of progression to MALE [25, 26]. Supervised exercise therapy is the recommended initial treatment for stable symptomatic PAD [19]. The CLEVER study was a randomised controlled trial that demonstrated supervised exercise therapy to have comparable efficacy to stent revascularisation, in the setting of intermittent claudication due to aortoiliac disease. However, there are challenges with implementing a supervised exercise program, which would preclude most patients. In the CLEVER study, 999 patients were screened in order to find 119 eligible participants [44]. Some significant barriers to supervised exercise include a lack of availability, transport accessibility, and compliance. Many patients with intermittent claudication can have other comorbidities that impede training [147]. Peripheral artery revascularisation is sometimes the only possible option to resolve lifestyle-limiting claudication. In this setting, the long-term risk of mortality, MALE and other limb events need to be weighed against this potential benefit and discussed with the patient.

Consistent with findings in chapter 4 and 5, male gender was independently associated with an 8% higher rate of MALE or mortality. In chapter 4, the meta-analysis showed that male gender was associated with a 13% adjusted increase in all-cause mortality. This divergence in

outcome was potentially more significant in advanced diseases, such as CLI or those treated with revascularisation. The secondary analysis implied that gender differences in mortality were at least partly attributable to cardiovascular-related events. However, this was at odds with coronary artery disease, where most observed gender differences in long-term mortality become attenuated when adjusting for age [178]. In ACCELERATE, male gender was significantly associated with higher adjusted mortality, but not major adverse cardiovascular events. These observations pointed to limb-related issues as an explanation. Prior epidemiological studies have found that there are more women with PAD than men in high-income countries [2]. Our dataset drew from comprehensive hospital records across Australia and New Zealand, and significantly fewer females were treated than males, especially with open surgery. Therefore, the selection of patients for revascularisation appeared to differ, according to gender, and this could be benefitting women. To test this hypothesis, we would also need to evaluate the clinical outcomes of the men and women with PAD that were managed conservatively. Further research into revascularisation decisions, relating to gender, is required.

Other predictors of MALE or mortality included older age, the presentation with CLI, a history of PAD or lower limb amputation, and medical comorbidities. Surprisingly, some cardiovascular history appeared to be protective, such as a prior percutaneous coronary intervention or coronary artery bypass graft operation. This thesis has described the robust relationship between PAD and coronary artery disease. The observations in this chapter could be revealing an advantage from completed coronary revascularisation, as it precedes a lower extremity intervention. A history of cerebrovascular disease also appeared to be beneficial. Patients with these other atherosclerotic conditions were potentially being treated more intensively with preventative treatments.

Advanced cancer was associated with a more than 2-fold increased likelihood of MALE or mortality, although we did not delineate between these endpoints. Cancer is a prothrombotic

condition, but a connection with MALE has not been established [248]. The associations between several non-PAD comorbidities and MALE or mortality were substantial, indicating that there are likely to be multiple contributing mechanisms. These findings underscore the multidisciplinary needs of these patients, which continues well beyond revascularisation.

Our study has some caveats worth noting. This was a retrospective evaluation of administrative data, which has the potential for coding and data entry inaccuracies. While propensity-score matching was performed, the possibility of unmeasured confounders cannot be excluded. Clinical information on lower limb disease related to anatomical and lesion characteristics, smoking, and medication use was unavailable. It is uncertain how these factors affected patient selection, where the endovascular approach was overwhelmingly preferred. Despite these limitations, there is evidence that broader details of demographics and medical comorbidities, can correlate with patterns of vascular disease [27, 249, 250]. This study compared revascularisation outcomes by focusing on MALE, mortality, and other less-severe adverse events. Some results, including quality of life, and walking impairment, were not captured. There are upcoming randomised clinical trials that will compare endovascular and surgical revascularisation by evaluating various clinical endpoints, and these will be less affected by confounding [121, 251]. Nevertheless, the strength of our data is in the heterogeneity of the study population, as this is likely to reflect current real-world practice better than clinical trials where participation is subject to recruitment and eligibility.

6.5. Conclusions

Endovascular lower extremity revascularisation was associated with a 14% higher likelihood of all-cause mortality, 49% greater urgent endovascular reintervention, and comparable rates of MALE to open surgery. The incidence of MALE or mortality for the overall cohort was very

high, which indicate the limitations of both strategies and the importance of ongoing multidisciplinary care. Personalised clinical decisions should dictate management, including consideration for conservative options. New procedures and medications are required to alter the clinical course of PAD in these advanced stages.

6.6 Acknowledgements

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6.7. Supplemental material

Table 6.5: Clinical characteristics of propensity-matched groups

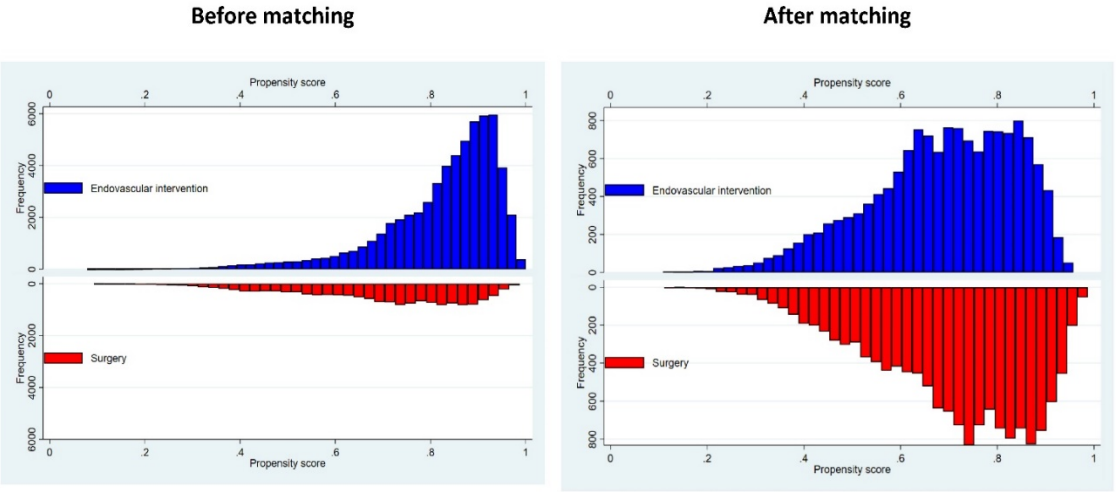
Baseline characteristics	Overall		Surgical		Endovascular		Standardised difference of the mean (%) /variance ratio
	N = 29,120		N = 14,560		N = 14,560		
	N	%	N	%	N	%	
Age (mean ± SD), y	71.0 ±11.8		71.0 ±11.5		71.0 ±12.2		1.11*
18-54	2,736	9.4	1,231	8.5	1,505	10.3	0.5
55-64	5,392	18.5	2,720	18.7	2,672	18.4	
65-74	9,033	31.0	4,699	32.3	4,334	29.8	
75-84	8,628	29.6	4,384	30.1	4,244	29.2	
85+	3,331	11.4	1,526	10.5	1,805	12.4	
Male	21,152	72.6	10,599	72.8	10,553	72.5	0.7
Presenting characteristics							
Elective	22,287	76.5	11,385	78.2	10,902	74.9	8.0
CLI	8,738	30.0	4,171	28.7	4,567	31.4	6.0
Private hospital	8,189	28.1	4,368	30.0	3,821	26.2	7.9
Presenting region							
-NSW/ACT	7,312	25.1	3,413	23.4	3,899	26.8	Reference
-VIC	7,069	24.3	3,739	25.7	3,330	22.9	6.5
-QLD	5,728	19.7	3,010	20.7	2,718	18.7	5.4
-SA/NT	1,873	6.4	917	6.3	956	6.6	1.2
-TAS	285	1.0	143	1.0	142	1.0	0.1
-WA	1,513	5.20	824	5.66	689	4.7	3.2
-NZ	5,340	18.3	2,514	17.27	2,826	19.4	6.2
Vascular history							
Vascular disease	13,473	46.3	6,428	44.2	7,045	48.39	9.2
Prior intervention	2,048	7.0	953	6.6	1,095	7.5	4.2
Lower limb amputation	1,494	5.1	675	4.6	819	5.6	4.6
Other cardiovascular history							
Acute coronary syndrome	1,478	5.1	680	4.7	798	5.5	3.7
Ischemic heart disease	3,572	12.3	1,683	11.6	1,889	13.0	4.5
Hypertension	10,312	35.4	4,921	33.8	5,391	37.0	6.9
Congestive heart failure	2,313	8.0	1,079	7.4	1,234	8.5	4.0
Valvular and rheumatic heart disease	797	2.7	373	2.56	424	2.9	2.3
Arrythmia or conduction system disorder	2,351	8.1	1,126	7.7	1,225	8.4	2.5
Stroke and cerebrovascular diseases	1,035	3.6	482	3.3	553	3.8	2.8
Coronary angiogram	2,211	7.6	1,030	7.1	1,181	8.1	4.1
PCI	634	2.2	299	2.1	335	2.3	1.7
CABG	455	1.6	207	1.4	248	1.7	2.5
Other comorbidities							
Diabetes	8,415	28.9	4,000	27.5	4,415	30.3	6.3
Major and metastatic cancer	545	1.9	262	1.8	283	1.9	1.1
Other cancers and tumours	2,087	7.2	977	6.7	1,110	6.6	3.6
Chronic lung disease	1,709	5.9	812	5.6	897	6.2	2.7
Pneumonia	1,466	5.0	701	4.8	765	5.3	2.1
Renal failure	2,666	9.2	1,252	8.6	1,414	9.7	3.8
Anemias and blood disease	5,408	18.6	2,534	17.4	2,874	19.7	6.6
Chronic liver disease	147	0.5	72	0.5	75	0.5	0.3
Dementia	610	2.1	293	2.0	317	2.2	1.1

Psychiatric disorders	936	3.2	423	2.9	513	3.5	3.8
Paralysis and functional disorders	2,067	7.1	957	6.6	1,110	7.6	4.2
Malnutrition	1,294	4.4	604	4.2	690	4.7	3.0
HIV/AIDS	36	0.1	19	0.1	17	0.1	0.4
Other significant endocrine and metabolic disorder	748	2.6	347	2.4	401	2.8	2.5
Disorder of fluid and electrolytes	2,236	7.7	1,061	7.3	1,175	8.1	2.9
Other endocrine/metabolic disorder	4,383	15.1	2,054	14.1	2,329	16.0	5.7
Inflammatory bowel disease	61	0.2	24	0.2	37	0.3	2.2
Bone/ joint muscle infection/ necrosis	932	3.2	427	2.9	505	3.5	3.0
Rheumatoid arthritis and inflammatory connective tissue disease	294	1.0	133	0.9	161	1.1	1.9
Disorder of the vertebrae and spinal disc	367	1.3	176	1.2	191	1.3	0.9
Osteoarthritis of hip or knee	313	1.1	147	1.0	166	1.1	1.2
Parkinson and Huntington's disease	70	0.2	34	0.2	36	0.3	0.3
Seizure and convulsion	134	0.5	64	0.4	70	0.5	0.6
Artificial openings for feeding for elimination	207	0.7	95	0.7	112	0.8	1.5

CABG, coronary artery bypass grafting; CLI, critical limb ischaemia; CTD, connective tissue disease; PCI, percutaneous coronary intervention; RA, rheumatoid arthritis

**variance ratio*

Figure 6.4: Distribution of propensity scores before and after matching



CHAPTER 7: HDL-MEDIATED CHOLESTEROL EFFLUX CAPACITY AND PAD IN INDIGENOUS AUSTRALIANS – THE HEART OF THE HEART STUDY

ABSTRACT

Background: There is a high prevalence of low high-density lipoprotein (HDL) cholesterol and cardiovascular disease in Indigenous Australians. A previous study found qualitative abnormalities of HDL in this population when they were compared with other non-Indigenous Australians. While dysfunctional HDL is an emerging risk factor for major adverse cardiovascular events (MACE), whether this translates to peripheral artery disease (PAD) has not been elucidated.

Methods: Heart of the Heart (HotH) was a cross-sectional study of Indigenous populations in Central Australia. A total of 185 participants underwent an extensive clinical assessment, which included an ankle-brachial index (ABI) and a blood test. An ABI ≤0.9 or >1.40 was abnormal, and 0.9 <ABI <1.0 was considered borderline. Comparisons were made between normal and abnormal ABI because this clearly distinguished between PAD-affected people. Lipid studies [total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C, and triglyceride], apolipoprotein A-I (apoA-I), apolipoprotein B (apoB) and HDL-mediated cholesterol efflux capacity (HDL CEC) [total HDL, ATP-binding cassette transporter A1 (ABCA1), and non-ATP-binding cassette transporter A1 (non-ABCA1)] were measured. The demographics, comorbidities, risk factor control, medication use and laboratory parameters of people with normal and abnormal ABI were compared.

Results: Of 185 participants, 107 had a normal ABI, 51 had an abnormal ABI, and 27 had borderline ABI. People with abnormal ABI were more likely to have metabolic syndrome (47% vs 31%, p=0.047), but were less likely to smoke (26% vs 42%, p=0.04), compared to those with normal ABI. Otherwise, both groups had comparable demographics, body mass index, medical comorbidities, and medication use. The lipid profile, including HDL-C levels, and apoA-I did not differ. Despite these similarities, the people with abnormal ABI had a lower

median total HDL CEC (30.6% [27.3, 34.2] and 31.1% [29.5, 34.2], p=0.02). There was a significantly lower adjusted total HDL CEC (adjusted difference -1.40%, 95% CI, -2.46 to -0.24, p=0.02) and ABCA-1 CEC (adjusted difference -1.20%, 95% CI, -2.11 to -0.19, p=0.02), when comparing abnormal with normal ABI. The difference in non-ABCA1 CEC was not statistically significant (adjusted difference -0.20%, 95% CI, -0.41 to 0.00, p=0.06).

Conclusions: HotH participants with early evidence of PAD demonstrated lower HDL CEC. These qualitative differences in HDL were observed, despite no difference in HDL-C levels. This has potential mechanistic implications underscoring a role for dysfunctional HDL in the pathogenesis of PAD. Further research is needed to determine whether this association has any prognostic significance or can be susceptible to therapeutic modification.

7.1. Introduction

There is a far higher incidence of cardiovascular disease in Indigenous Australians when compared with other Australians [252]. Major adverse cardiovascular events (MACE) account for approximately one-third of an almost 20-year gap in life expectancy that has been reported [253]. These health disparities are not well understood or easily explained by differences in the prevalence of conventional risk factors, such as hypertension, dyslipidaemia, or obesity [145].

Peripheral artery disease (PAD) is increasingly recognised as a high-risk condition with a clinical course that differs from other manifestations of atherosclerotic cardiovascular disease [93]. The presence of PAD is associated with disproportionately high event rates compared with other vascular groups [223], and this has become a focal point for studies of new medical therapies [147].

Low high-density lipoprotein cholesterol (HDL-C) levels have an established association with the development of symptomatic PAD [15, 124, 125]. A high prevalence of low HDL-C has also been observed in Indigenous populations [254, 255]. Despite a compelling link between low HDL-C and cardiovascular disease [256], medical therapies that increase HDL-C levels have not been demonstrated to improve clinical outcomes [257]. Attention has shifted to measures of HDL function, including HDL-mediated cholesterol efflux capacity (HDL CEC), among other functions [257, 258]. In one observational study, HDL CEC was an independent predictor of MACE, whereas HDL-C levels corresponded with other conventional risk factors. People with the highest quartile HDL CEC had a 67% lesser incidence of MACE, compared with those in the lowest quartile [259]. While dysfunctional HDL is an emerging risk factor for MACE, whether this translates to PAD has not been elucidated.

Heart of the Heart (HotH) was a cross-sectional study of Indigenous populations in Central Australia. Participants underwent extensive clinical assessment, which included an

ankle-brachial index (ABI) and a blood test for many laboratory parameters. It was previously shown that HDL CEC was reduced in Indigenous Australians from HotH when they were compared with a matched group of other Australians [260]. Here we compared the Indigenous Australians with early evidence of PAD to those without, to see whether there were qualitative differences in HDL.

7.2. Methods

7.2.1. Study design

HotH was a cross-sectional study of Indigenous populations within Central Australia, which was conducted between May 2008 and November 2009. The study design and data collection have been previously published [261, 262]. Participants were eligible if they were aged ≥18 years; self-reported as Indigenous residents of Central Australia; and were able to provide informed consent. In total, 436 volunteers underwent comprehensive clinical assessment, inclusive of 185 participants who had a screening ankle-brachial index and frozen blood samples. This study complied with the Declaration of Helsinki and was approved by the Central Australian Human Research Ethics Committee and the Monash University Standing Committee on Ethics in Research Involving Humans.

7.2.2. Data collection

Participants underwent a structured interview. The details obtained included age; residence; socioeconomic status – income, education, employment; smoking status; alcohol intake; past medical history and current medications. Self-reported medical history was later corroborated with medical records. The participants underwent measurements of blood pressure, height,

weight, abdominal and hip circumference. Blood pressure was taken after the participant had been seated for 5 minutes. Participants completed a Rose angina questionnaire [263] and underwent electrocardiography (ECG). Non-fasting venous blood was taken, and plasma/serum was stored at -80°C after centrifugation until required. Laboratory tests included lipid studies, glycosylated haemoglobin (HbA1c), renal, thyroid and liver function, full blood count, high-sensitivity C-reactive protein (hs-CRP), asymmetric dimethylarginine (ADMA), and B-type natriuretic peptide (BNP). The total cholesterol, low-density lipoprotein cholesterol (LDL-C), HDL-C, triglycerides, apolipoprotein A-I (apoA-I), and apolipoprotein B (apoB) were analysed using a COBAS Integra 400 analyser (Roche Diagnostics, Basel, Switzerland). A spot urine sample was tested for urine albumin-creatinine ratio (ACR).

7.2.3. Study aims

This analysis aimed to (1) compare demographics, clinical characteristics, and laboratory parameters of people with normal ABI and abnormal ABI, and (2) evaluate for differences HDL-mediated cholesterol efflux capacity, independent of other measured variables.

7.2.4. Definitions of comorbidities

At-risk alcohol drinking was the consumption of more than two standard drinks per day [264]. Hypertension was defined by a measurement of systolic blood pressure (BP) >140 mmHg or diastolic BP >90 mmHg. Abnormal non-fasting lipid levels were characterised by a: total cholesterol ≥5.5 mmol/L, LDL-C ≥3.5 mmol/L, HDL-C <1.0 mmol/L for male and <1.3 mmol/L for female, and triglycerides ≥2.0 mmol/L. An HbA1c ≥6.5% was consistent with a diagnosis of diabetes mellitus. Obesity was recognised as a body mass index (BMI) ≥ 30 kg/m^2, or waist circumference >102 cm in males and >88cm in females. Metabolic syndrome was

defined based on the World Health Organisation criteria after adjusting TG levels for non-fasting status [265]. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 and/or urine ACR >2.5 mg/mmol for men and >3.5 mg/mmol for women or a documented history of CKD [266]. Pre-existing coronary artery disease was definitive angina on the Rose angina questionnaire, prior acute coronary syndrome, positive coronary angiography, or evidence of Q-waves on ECG (reviewed by two independent investigators). Pre-existing cardiovascular disease was the presence of rheumatic heart disease, non-rheumatic valvular disease, atrial fibrillation, heart failure, coronary artery disease (as defined above), peripheral artery disease or cerebrovascular disease.

7.2.5. Measurement of the ankle-brachial index

Certified technicians measured ankle and brachial systolic blood pressures with a handheld Doppler device. The ankle-brachial pressure index was calculated by dividing blood pressure in the ankle by the highest of two blood pressure readings in the arms. The index was recorded for each participant on both arms and the left leg. Assessments were performed using a portable Hadeco Bidirectional Smartdop 20 doppler ultrasound machine (Hayashi Denki Co., Kawasaki, Japan). An ABI ≤0.9 or >1.40 was abnormal, and 0.9 <ABI <1.0 was considered borderline [19].

7.2.6. Measurement of HDL-mediated cholesterol efflux capacity

Total HDL, ATP-binding cassette transporter A1 (ABCA1), and non-ABCA1-mediated CEC were measured using apolipoprotein B (apoB)-depleted serum samples. ApoB-containing lipoproteins were depleted with polyethylene glycol (Sigma, St. Louis, MO, USA) as has been previously described [267]. After labelling with BODIPY-cholesterol (Avanti Polar Lipids,

Alabaster, AL, USA) and upregulating ABCA1 expression by cAMP treatment, RAW 264.7 macrophages were incubated with 1.4% apo B-depleted serum for 4h [268, 269]. The fluorescence intensity (FI) of the cell media and cell lysates was measured at Ex/Em 485/535 nm using a Perkin Elmer Victor 3 plate reader (Perkin-Elmer, Wellesley, MA, USA). HDL-mediated CEC was determined as follows:

$$\text{CEC (\%)} = \frac{\text{Media FI at 4h}}{\text{Media FI at 4h + Cell Lysate FI at 4h}} \times 100$$

Total HDL/non-ABCA1-mediated CEC was defined as the CEC in cAMP treated/non-treated cells. In contrast, ABCA1-mediated CEC was calculated as the difference between the per cent efflux in cAMP treated cells and that of cAMP non-treated cells. All assays were performed in duplicate.

7.2.7. Statistical analysis

Data were analysed for normal distribution using the Shapiro-Wilk test. Continuous parameters were expressed as median (interquartile range: IQR) and compared using unpaired t-test or Mann-Whitney U test if not normally distributed. Categorical variables were expressed as numbers and percentages and compared using the Chi-square test. Differences between ABI groups for continuous parameters were tested using the one-way analysis of variance (ANOVA) test. Significant differences between ABI groups were included for the adjustment by using analysis of covariance (ANCOVA), in order to compare HDL CEC. Multivariate linear regression analyses were performed to test the association between ABI and HDL CEC. This included demographics, medical history, medications, socioeconomic status, risk factor control, lipid parameters, and other laboratory parameters. Multicollinearity among variables was checked before a variable was included in the final model. A two-sided p value of less than

0.05 was considered significant. All statistical analyses were conducted using Stata 14.2 version (StataCorp, College Station, TX, USA).

7.3. Results

7.3.1. Participant characteristics according to ankle-brachial index

Of 185 participants, there was 107 (58%) normal, 51 (28%) abnormal ABI, and 27 (15%) borderline ABI. The characteristics of people with normal ABI and abnormal ABI are summarised in Table 7.1. People with abnormal ABI were more likely to have metabolic syndrome (47% vs 31%, p=0.047), but were less likely to currently smoke (26% vs 42%, p=0.04), compared to those with normal ABI. Otherwise, both groups had comparable demographics, BMI, pre-existing medical comorbidities, and use of medications.

7.3.2. Laboratory parameters according to ankle-brachial index

The laboratory parameters of people with normal and abnormal ABI are outlined in Table 7.2. The total cholesterol, LDL-C, apoA-I, HDL-C levels did not differ between normal and abnormal ABI groups. There were significant differences in the median total HDL-mediated CEC (31.1% [29.5, 34.2] and 30.6% [27.3, 32.7], p=0.02), ABCA1-mediated CEC (22.1% [20.7, 24.8] and 21.6% [18.6, 23.4], p=0.02), and non-ABCA1-mediated CEC (9.1% [8.7, 9.5] and 8.8% [8.4, 9.4], p=0.04), for normal and abnormal ABI, respectively. ADMA was significantly lower in normal ABI, compared with abnormal ABI (0.53 [0.47, 0.60] μmol/L and 0.57 [0.50, 0.64] μmol/L, p=0.04). Other non-lipid laboratory parameters, including hs-CRP, HbA1c, and eGFR, were comparable between groups.

Table 7.1: Participant characteristics and comorbidities according to ABI

Characteristic	Normal ABI (N = 107)	Abnormal ABI (N =51)	p value
Age, median (IQR)	46.0 (33.0, 54.0)	46.0 (30.0, 51.0)	0.43
Male, N (%)	46 (43.0)	21 (41.2)	0.83
BMI, kg/m2 (IQR)	28.0 (25.5, 31.0)	28.8 (25.8, 33.7)	0.09
Obesity, N (%)	60 (56.1)	33 (64.7)	0.30
SBP, mmHg (median, IQR)	126.0 (116.0, 141.0)	132.0 (119.0, 142.5)	0.17
DBP, mmHg (median, IQR)	80.0 (73.5, 88.5)	83.5 (72.5, 88.5)	0.79
History, N (%)			
Hypertension	56 (52.3)	30 (58.8)	0.44
Diabetes	36 (33.6)	25 (49.0)	0.06
Dyslipidaemia	98 (91.6)	49 (96.1)	0.30
CKD	42 (39.3)	20 (39.2)	1.00
Metabolic syndrome	33 (30.8)	24 (47.1)	0.04
Current smoker	45 (42.1)	13 (25.5)	0.04
At-risk alcohol drinking	54 (50.5)	25 (49.0)	0.86
Depression	20 (18.7)	5 (10.0)	0.17
Pre-existing CAD	11 (10.3)	6 (11.8)	0.78
Pre-existing CVD	22 (20.6)	8 (15.7)	0.47
Medications, N (%)			
Antihypertensive	30 (28.0)	16 (31.4)	0.67
Lipid-lowering	30 (28.0)	15 (29.4)	0.86
Diabetes	21 (19.6)	14 (27.5)	0.27
Insulin	22 (20.6)	15 (29.4)	0.22
Antidepressant	6 (5.6)	4 (7.8)	0.59
Education status			
Education Attainment	8 (7.8)	2 (4.0)	0.61
Non-Advanced education	36 (35.0)	20 (40.0)	
Advanced education	59 (57.3)	28 (56.0)	
Employment status			
Unemployed	64 (62.7)	25 (50.0)	0.07
Part-time/ Casual	17 (16.7)	6 (12.0)	
Full time	21 (20.6)	19 (38.0)	
Income (fortnightly)			
$AU 0-199	8 (7.8)	4 (8.0)	0.19
$AU 200-399	42 (41.2)	21 (42.0)	
$AU 400-599	24 (23.5)	5 (10.0)	
$AU 600-799	8 (7.8)	10 (20.0)	
$AU 800-999	5 (4.9)	2 (4.0)	
$AU >1000	15 (14.7)	8 (16.0)	

Age, BMI, SBP and DBP expressed as median and interquartile range (IQR). ABI, ankle-brachial index; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 7.2: Laboratory parameters according to ABI

Characteristic	Normal ABI (N=107)	Abnormal ABI (N=51)	p value
Lipid Parameters (median)			
Total cholesterol, mmol/L	4.60 (3.96, 5.51)	4.65 (3.70, 5.54)	0.85
LDL-C, mmol/L	2.62 (2.11, 3.51)	2.73 (1.94, 3.85)	0.60
HDL-C, mmol/L	0.92 (0.69, 1.11)	0.92 (0.77, 1.12)	0.87
TG, mmol/L	2.01 (1.38, 2.89)	1.85 (1.25, 2.77)	0.53
ApoA-I, mmol/L	1.31 (1.10, 1.55)	1.39 (1.18, 1.56)	0.34
ApoB, mmol/L	0.77 (0.63, 0.95)	0.75 (0.62, 1.02)	0.94
HDL-C/ApoA-I ratio	0.69 (0.61, 0.78)	0.67 (0.61, 0.79)	0.57
Total HDL CEC	31.1 (29.5, 34.2)	30.6 (27.3, 32.7)	0.02
ABCA1 CEC	22.1 (20.7, 24.8)	21.6 (18.6, 23.4)	0.02
Non-ABCA1 CEC	9.1 (8.7, 9.5)	8.8 (8.4, 9.4)	0.04
Other Parameters (median)			
Hs-CRP, mg/L	4.40 (2.00, 8.00)	3.40 (2.00, 8.20)	0.72
HbA1c, %	6.10 (5.70, 6.60)	6.35 (5.90, 8.10)	0.10
Urine ACR, mg/mmol	1.45 (0.60, 5.70)	1.90 (0.70, 12.60)	0.23
eGFR, mL/min/1.73m2	101.00 (86.80, 116.20)	97.30 (83.10, 110.70)	0.18
ADMA, µmol/L	0.53 (0.47, 0.60)	0.57 (0.50, 0.64)	0.04
BNP, pg/mL	7.60 (5.00, 15.60)	6.45 (5.00, 22.30)	0.99

Values expressed as median and interquartile range (IQR). ABCA1 CEC, ATP-binding cassette transporter A1-mediated cholesterol efflux capacity; ACR, albumin-creatinine ratio; ADMA, asymmetric dimethylarginine; ApoA-I, apolipoprotein A-I, ApoB, apolipoprotein B; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; HDL CEC, high-density lipoprotein-mediated cholesterol efflux capacity; Hs-CRP, high sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride

7.3.3. HDL-mediated cholesterol efflux capacity according to ankle-brachial index

Table 7.3 summarises the HDL-mediated CEC in people with normal and abnormal ABI. Adjusted analysis of HDL-mediated CEC was performed, which corrected for the group differences in metabolic syndrome, current smoker, and ADMA levels. When adjusting for these differences, there was a significantly lower total HDL-mediated CEC (adjusted difference, -1.40%, 95% CI, -2.46 to -0.24, p=0.02) and ABCA1-mediated CEC (adjusted difference, -1.20%, 95% CI, -2.11 to -0.19, p=0.02) in people with abnormal ABI, compared with normal ABI. The differences in non-ABCA1-mediated CEC were not statistically significant (adjusted difference, -0.20%, 95% CI, -0.41 to 0.00, p=0.06).

Table 7.3: Comparison of HDL-mediated cholesterol efflux capacity between normal ABI and abnormal ABI group

	Unadjusted			Adjusted*			
Characteristic	Normal ABI (N = 107)	Abnormal ABI (N = 51)	p value	Difference†	95% CI	95% CI	p value
Total HDL CEC, %	31.1 (29.5, 34.2)	30.6 (27.3, 32.7)	0.02	-1.40	-2.46	-0.24	0.02
ABCA1 CEC, %	22.1 (20.7, 24.8)	21.6 (18.6, 23.4)	0.02	-1.20	-2.11	-0.19	0.02
Non-ABCA1 CEC, %	9.1 (8.7, 9.5)	8.8 (8.4, 9.4)	0.04	-0.20	-0.41	0.00	0.06

** Differences between the groups: metabolic syndrome, current smoker, and ADMA levels were included for the adjustment using ANCOVA. †vs normal ABI group. Values are median (interquartile range). ABCA1 CEC = ATP-binding cassette transporter A1-mediated cholesterol efflux capacity, ANCOVA = analysis of covariance, non-ABCA1 CEC = non-ATP-binding cassette transporter A1-mediated cholesterol efflux capacity, Total HDL CEC = total high-density lipoprotein-mediated cholesterol efflux capacity.*

7.4. Discussion

The HotH study sought to determine the prevalence of cardiovascular risk factors and evidence of manifest vascular disease in a well-phenotyped cohort of Indigenous Australians. This is particularly important given the documented premature cardiovascular risk that is reported in this population. We demonstrated that more than one-quarter of participants had an abnormal ABI, many of whom had an otherwise low prevalence of established cardiovascular risk factors. While many such risk factors did not associate with the presence of a low ABI, we did demonstrate that this group with early evidence of PAD demonstrated lower cholesterol efflux capacity. Prior studies have found HDL-C and apoA-I levels to correlate with cholesterol efflux capacity [270, 271]. Here, qualitative differences in HDL were observed, despite no difference in HDL-C or apoA-I levels. This has potential mechanistic implications underscoring a role for dysfunctional HDL in the pathogenesis of PAD.

These findings extend reports of an association between lower cholesterol efflux capacity and cardiovascular risk to the setting of PAD. It remains to be determined whether this association reflects a mechanistic influence on the peripheral vasculature, has any prognostic significance or may be susceptible to therapeutic modification [272]. PAD has an accepted association with cardiovascular morbidity and mortality, for which new treatments are required [223]. LDL-C lowering through the use of statins and protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are effective in reducing MACE and major adverse limb events [86, 89, 93]. In the FOURIER study, a linear relationship was seen with LDL-C lowering through PCSK9 inhibition and the relative risk reduction in major adverse limb events, which continued even for LDL-C levels <10 mg/dL (0.26 mmol/L) [93]. With the combination of statins and PCSK9-inhibitors being potent LDL-C lowering agents, other approaches to lipid management are also being researched [135]. High cholesterol efflux capacity has been reported to associate with less mortality in patients six years following

myocardial infarction [129]. The infusion of reconstituted HDL mimetics in patients following myocardial infarction has been demonstrated to increase cholesterol efflux capacity [130], and the effects of this mimetic on cardiovascular events are now being investigated in a large clinical trial [131]. The proof-of-concept for treating PAD patients with reconstituted HDL mimetics was researched by an in vivo human study. A single infusion of HDL mimetic led to a visible reduction in the lipid and inflammatory composition of atherosclerosis, thereby appearing to stabilise the morphology of plaque in the peripheral artery [273]. Given these collective findings, a subgroup analysis of PAD in clinical trials of HDL mimetics would be of interest.

The relationship between conventional risk factors and PAD is distinct from other atherosclerotic conditions [16]. Smoking appears to have a more substantial impact in PAD pathogenesis, whereas the effects of hypertension and elevated LDL-C, correlate less, than with coronary artery disease [1, 16, 17]. In an exploratory analysis of the Women's Health Study, the lipid particle characteristics of 110 participants that developed symptomatic PAD during follow-up were compared with 27,778 unaffected women. Both groups had comparable total cholesterol and LDL-C levels. However, PAD-affected women had higher LDL and very-low-density lipoprotein particle concentrations, raised triglyceride-rich lipoprotein levels, as well as lower HDL-C levels and HDL particle concentrations [15]. The constitution of their lipids was vastly different to patients with atherosclerosis of the coronary and cerebrovascular circulation, where apoB and LDL-C levels have a predominant role [15, 16]. Overall, the Women's Health Study raised questions about the role of lipid abnormalities in the pathophysiology of PAD. We further these observations to a connection between lower cholesterol efflux capacity and early evidence of PAD.

There are clinical differences between PAD and other manifestations of atherosclerotic cardiovascular disease, which have potential relevance to cholesterol efflux capacity. Walking

impairment is a prominent feature of PAD that can affect people even in the before the development of intermittent claudication [4, 5, 18]. In individuals without pre-existing cardiovascular disease, exercise has been related to increases in cholesterol efflux capacity [274]. One study of coronary artery disease patients that underwent exercise rehabilitation and lifestyle modification, there were observed increases in cholesterol efflux for those that accomplished the highest maximum workloads [270]. In PAD patients, there were no changes in HDL functionality seen after they performed a 24-week supervised exercise program. One hypothesis suggested by the authors of this study was that PAD limited exercise intensity to levels that could lead to appreciable improvements in HDL functionality [275]. The association between physical activity and cholesterol efflux could be significant in the PAD setting, although this has yet to be demonstrated.

Some limitations should be noted regarding this cross-sectional study. Although significant discrepancies in cholesterol efflux capacity were observed across patient groups, the absolute differences were relatively small. Multivariate logistic regression accounted for a wide range of clinical information; however, the potential for unmeasured confounders cannot be excluded. PAD was identified using an ABI. While this investigation has good sensitivity and specificity for PAD [276], more limb-specific details relating to signs and symptoms were not assessed. Only one lower limb was screened, thereby reducing sensitivity for overall disease detection. No conclusions can be drawn regarding the influence of cholesterol efflux capacity on peripheral vasculature without longitudinal data. The laboratory methods used to measure HDL function can differ, and currently, there is no consensus on what the gold standard should be [129, 267]. To better understand the relationship between cholesterol efflux capacity and PAD, cohort studies with limb-specific clinical information are needed. Nevertheless, the limitations of this study should be considered in light of the inherent

challenges with researching scattered populations in the remote communities of Central Australia.

7.5. Conclusions

In the HotH study, there was a significant association between an abnormal ABI and reduced cholesterol efflux capacity. These qualitative differences in HDL were observed, despite no difference in HDL-C or apoA-I levels and many conventional cardiovascular risk factors. Previous studies have demonstrated an association between dysfunctional HDL and MACE, but this is the first to identify a link with PAD. Further research is needed to determine whether this association has any prognostic significance or can be susceptible to therapeutic modification.

7.6. Acknowledgements

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CHAPTER 8: ANKLE-BRACHIAL INDEX SCREENING FOR INDIGENOUS AUSTRALIANS – THE HEART OF THE HEART STUDY

ABSTRACT

Background: The early stages of peripheral artery disease (PAD) are frequently asymptomatic and under-diagnosed, which makes it difficult to approximate the actual prevalence in Australia. There are striking health disparities that affect young Indigenous people, and the estimation of cardiovascular risk is especially problematic. The usefulness of screening this population for early PAD with an ankle-brachial index (ABI) has not been evaluated.

Methods: Heart of the Heart (HotH) was a cross-sectional study of Indigenous populations in Central Australia. A total of 185 participants underwent an extensive clinical assessment, which included an ABI and measurement of cardiovascular risk factors, inclusive of age, systolic blood pressure (BP), smoking status, total cholesterol, high-density lipoprotein cholesterol (HDL-C) and diabetes. The risk profile of people with normal ABI was compared to those with non-normal (borderline or abnormal) ABI. For those with non-normal ABI and no pre-existing cardiovascular disease, Framingham-based equations were applied to estimate the five-year risk of a major adverse event. These participants were classified as very low (<5%), low (5-9.9%), moderate (10-15%), and high risk (>15%).

Results: Of 185 people, 58% had normal, 28% abnormal, and 15% borderline ABI. When comparing normal with non-normal ABI, both groups were of similar age, gender, history of hypertension, diabetes, and pre-existing coronary artery disease and cardiovascular disease. There was higher smoking in people with normal ABI. Otherwise, both groups had comparable risk factor control and the use of cardiovascular preventative therapies. When applying the National Vascular Disease Prevention Alliance algorithm to non-normal ABI, the proportion of people that were very low, low, moderate and high risk was 53%, 16%, 8% and 23%, respectively.

Conclusions: A considerable portion of Indigenous participants screened had evidence of PAD, and their cardiovascular risk was seemingly underestimated through conventional methods. These results raise the possibility that undiagnosed PAD is contributing to health disparities in Indigenous Australians. More extensive research is needed to confirm these findings, as the implications would be that the current national guidelines are deficient.

8.1. Introduction

The prevalence of PAD in Indigenous Australians and other Australians has not been well defined [252]. In other Western populations, approximately 3 to 10% of the non-Indigenous people are affected, and this increases to 20% of those above 70 years of age [7]. The difficulties arise in identifying early stages of PAD, which are frequently asymptomatic and under-diagnosed [4]. An ankle-brachial index (ABI) is a simple bedside test that has high sensitivity and specificity for PAD [19]. The introductory chapter described the natural history of patients found to have an abnormal or borderline ABI, compared to a normal ABI. Such evidence of PAD has significant implications regarding an individual's future risk of major adverse cardiovascular events and mortality. A meta-analysis combined sixteen population studies and showed that an abnormal ABI (≤0.90 or >1.40) was connected with increased mortality independent to the Framingham risk equation [20]. Despite these associations, the use of ABI screening for PAD is not recommended in national guidelines [143, 144]. Problems with underestimating cardiovascular risk are especially relevant to the young Indigenous community [277]. There is a 10 to 20-fold increased mortality in young Indigenous Australians, compared with their non-Indigenous counterparts [145]. Cardiovascular disease accounts for approximately one-third of an almost 20-year gap in life expectancy that has been reported [253].

In chapter 7, we demonstrated that more than one-quarter of Indigenous participants in the Heart of the Heart (HotH) study had an abnormal ABI, many of whom had an otherwise low prevalence of established cardiovascular risk factors. Here, the analysis is extended to all people with non-normal ABI (borderline or abnormal ABI). We applied accepted Framingham-based equations to see whether a non-normal and abnormal ABI provided additional risk-stratification. This chapter explores the potential implications of these findings concerning the management of young Indigenous Australians.

8.2. Methods

8.2.1. Study design and analysis

Details of the study design, data collection and statistical analyses were described in chapter 7. In brief, HotH was a cross-sectional study conducted from May 2008 to November 2009, examining Indigenous populations within Central Australia. Participants were eligible if they were aged ≥18 years; self-reported as Indigenous residents of Central Australia; and were able to provide informed consent. In total, 436 volunteers underwent comprehensive clinical assessment, inclusive of 185 participants who had a screening ABI and frozen blood samples. The participants were subject to an extensive clinical assessment with a structured interview and physical examination. Medical history and cardiovascular risk factors were confirmed by screening, as well as corroboration with medical documentation and medication history.

8.2.2. Study aims

This analysis aimed to (1) compare demographics, clinical characteristics, and laboratory parameters of people with normal ABI and non-normal ABI, and (2) apply accepted cardiovascular risk algorithms to participants with abnormal and non-normal ABI.

8.2.3. Definition of comorbidities

An ABI ≤0.9 or >1.40 was abnormal, and 0.9 <ABI < 1.0 was borderline. An ABI was considered non-normal if the result was abnormal or borderline. Hypertension was defined by a measurement of systolic blood pressure (BP) >140 mmHg or diastolic BP >90 mmHg. An HbA1c ≥6.5% was consistent with a diagnosis of diabetes mellitus. Pre-existing coronary artery disease was definitive angina on the Rose angina questionnaire, prior acute coronary

syndrome, positive coronary angiography, or evidence of Q-waves on ECG (reviewed by two independent investigators). Pre-existing cardiovascular disease was the presence of rheumatic heart disease, non-rheumatic valvular disease, atrial fibrillation, heart failure, coronary artery disease (as defined above), peripheral artery disease or cerebrovascular disease.

8.2.4. Risk calculation

Framingham-based equations were applied to estimate the five-year risk of people with non-normal or abnormal ABI that had no pre-existing cardiovascular disease. Two accepted equations were used. The National Vascular Disease Prevention Alliance (NVDPA) algorithm incorporates the following variables: gender, age (between 35 to 74), systolic blood pressure, smoking status, total cholesterol, HDL cholesterol, and diabetes [143]. In people with age outside the specified range, the closest qualifiable age was entered. An alternative Framingham equation [278] was applied, that utilised these same variables. This equation was validated for a cohort of 1,448 Indigenous Australians in Far North Queensland. Participants were classified as having a: very low (<5%), low (5-9.9%), moderate (10-15%), and high (>15%) five-year risk of an adverse cardiovascular event.

8.3. Results

8.3.1. Characteristics of participants according to ABI

Of 185 participants, there were 107 (58%) with normal and 78 with non-normal ABI. Non-normal ABI comprised of 51 (28% of total) abnormal and 27 (15% of total) borderline measurements. The characteristics of the people with normal and non-normal ABI are summarised in Table 8.1. Both normal and non-normal ABI groups had comparable median age (46 and 44, p=0.45), proportion of females (57.0% and 65.4%, p=0.25), hypertension

(52.3% and 57.7%, p=0.47), diabetes (33.6% and 44.9%, p=0.12), pre-existing coronary artery disease (10.3% and 9.0%, p=0.77) and cardiovascular disease (20.6% and 17.9%, p=0.66), respectively. People with normal ABI were more likely to smoke than those with non-normal ABI (42.1% vs 25.6%, p=0.02). Otherwise, both groups had comparable risk factor control regarding systolic and diastolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, high sensitivity C-reactive protein, and glycated haemoglobin. There was a similar use of cardiovascular preventative therapies.

8.3.2. Absolute cardiovascular risk categories of people with abnormal ABI

The estimated five-year risk of people with non-normal or abnormal ABI and no pre-existing cardiovascular disease is outlined in Table 8.2. When the NVDPA algorithm was applied to non-normal ABI, the proportion of people that were very low, low, moderate, and high-risk were 53%, 16%, 8%, and 23%, respectively. The alternative Framingham equation produced similar results, with the corresponding percentage of very low, low, moderate, and high-risk people as 50%, 14%, 13%, 23%. Applying the NVDPA algorithm to abnormal ABI, the proportion of people that were very low, low, moderate, and high-risk were 54%, 20%, 10%, and 22%, respectively. Using the alternative Framingham equation for abnormal ABI, the percentage of very low, low, moderate, and high-risk people was 49%, 15%, 17%, 24%, accordingly.

Table 8.1: Comparison of participants with normal and non-normal ABI

Characteristic	Normal ABI (N = 107)	Non-normal ABI (N = 78)	p value
Age, median (IQR)	46.0 (33.0, 54.0)	44.0 (30.0, 55.0)	0.45
Male, N (%)	46 (43.0)	27 (34.6)	0.25
BMI, kg/m2 (IQR)	28.0 (25.5, 31.0)	28.5 (25.5, 32.7)	0.35
Obesity, N (%)	60 (56.1)	48 (61.5)	0.46
SBP, mmHg	126.0	128.8	0.42
DBP, mmHg	80.0	83.3	0.94
History, N (%)			
Hypertension	56 (52.3)	45 (57.7)	0.47
Diabetes	36 (33.6)	35 (44.9)	0.12
Dyslipidaemia	98 (91.6)	76 (97.4)	0.10
CKD	42 (39.3)	32 (41.0)	0.81
Metabolic syndrome	33 (30.8)	33 (42.3)	0.11
Current smoker	45 (42.1)	20 (25.6)	0.02
Pre-existing CAD	11 (10.3)	7 (9.0)	0.77
Pre-existing CVD	22 (20.6)	14 (17.9)	0.66
Lipid Parameters (median)			
Total cholesterol, mmol/L	4.60	4.78	0.82
LDL-C, mmol/L	2.62	2.75	0.59
HDL-C, mmol/L	0.92	0.92	0.71
Triglycerides, mmol/L	2.01	1.86	0.54
Other Parameters (median)			
Hs-CRP, mg/L	4.40	4.00	0.95
HbA1c, %	6.10	6.20	0.29
eGFR, mL/min/1.73m^2	101.0	98.0	0.27
Medications, N (%)			
Antihypertensive	30 (28.0)	26 (33.3)	0.44
Lipid-lowering	30 (28.0)	25 (32.1)	0.56
Diabetes	21 (19.6)	21 (26.9)	0.24
Insulin	22 (20.6)	22 (28.2)	0.23

ABI, ankle-brachial index; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol, SBP, systolic blood pressure.

Table 8.2: Estimated 5-year risk of people with non-normal or abnormal ABI and no pre-existing cardiovascular disease

	Non-normal ABI (N = 64)	Abnormal ABI (N = 41)
NVDPA algorithm*		
Very low (<5% risk)	34 (53%)	22 (54%)
Low (5-9% risk)	10 (16%)	8 (20%)
Moderate (10-15% risk)	5 (8%)	4 (10%)
High (>15% risk)	15 (23%)	9 (22%)
Framingham equation^{+}		
Very low (<5% risk)	32 (50%)	20 (49%)
Low (5-9% risk)	9 (14%)	6 (15%)
Moderate (10-15% risk)	8 (13%)	7 (17%)
High (>15% risk)	15 (23%)	10 (24%)

** National Vascular Disease Prevention Alliance (NVDPA) algorithm [143] used to predict 5-year risk of cardiovascular disease.* $^{+}$ *Framingham equation calibrated for Indigenous Australians [278] used to predict 5-year risk of cardiovascular disease.*

8.4. Discussion

Nearly half of HotH participants had a non-normal ABI, which is concerning given the young age and high proportion of females screened. This contrasts with conventional reports that PAD is more common in older subjects [10, 140]. The Framingham-based risk algorithms appeared to be inadequate in this study. These results suggest there is a high prevalence of undiagnosed PAD in young Indigenous Australians. ABI screening could be indicated for this population, although this is not currently recommended in the national guidelines [143, 144].

The usefulness of ABI screening is dependent on the likelihood of detecting asymptomatic disease, and the potential for treatment to change consequently. The prevalence of PAD in Australia has not been well characterised, although there are two other noteworthy studies in this space [217, 279]. The REACH Registry was an international observational study that examined people with established cardiovascular disease or a minimum of three risk factors. In a subset of 2,489 Australians that underwent PAD screening, 28% were found to have an abnormal ABI. These Australians were appreciably older than the HotH group (mean age of 73 and 44, respectively) [217]. The DRUID study tested for PAD and other complications of diabetes in 135 Indigenous people that resided in urban areas of Australia. In this setting, 12% of participants were diagnosed with PAD (ABI <0.90), and this was a 3-fold higher incidence compared with other Australians, after accounting for age and risk factors [279]. HotH differed from DRUID because, in addition to people with diabetes, it also featured non-diabetic and seemingly low-risk Indigenous Australians that lived in remote Central Australia. Also, while most PAD studies focus solely on a low ABI, in this analysis, an ABI >1.40 was classified as abnormal. An elevated ABI is suggestive of non-compressible lower extremity arteries [19] and strongly correlates with increased cardiovascular-related and all-cause mortality [21, 140]. The HotH, REACH, and DRUID studies provide a snapshot of the

prevalence of PAD in different parts of Australia, but the problem needs to be better defined in larger populations [252].

PAD could be contributing to the lower life expectancy observed in Indigenous Australians. There were relatively fewer deaths and hospitalisations attributed to PAD for Indigenous Australians in 2007-2008, compared with other Australians [252]. However, the actual disease burden could be masked, as other causes of mortality might compete with PAD-attributed events. One prospective study compared cardiovascular outcomes in Indigenous and non-Indigenous Australians after a clinic review for PAD. The Indigenous patients were younger but had a nearly five-fold increase (HR 4.72, 95% CI, 1.41 to 15.78, p=0.01) in major adverse cardiovascular events, compared with other Australians [280]. Of the HotH participants with a non-normal ABI, 82% had no history of cardiovascular disease. Both the NVDPA algorithm [143] and alternative Framingham equation [278] classified most of them as low risk. In chapter 1, we outlined the natural history of people that have an abnormal or borderline ABI, compared to those with normal ABI. Given the recognised association between PAD and major adverse cardiovascular events [20, 140], the risk model recommended in the national guidelines appear inaccurate. Here, the assertion is that non-normal ABI reclassifies people into a high-risk category, which warrants an intensive medical and lifestyle intervention [147].

ABI is a simple and non-invasive test with good sensitivity and specificity for detecting PAD [19]. The use of this test to diagnose asymptomatic PAD has not been endorsed in Australia [144, 252], whereas the American Heart Association recommends screening for specific populations and age groups [19]. People diagnosed with PAD can benefit from preventative treatments [19, 61, 147]. Nevertheless, the use of ABI to guide the prescription of therapies could lead to over-treatment in some cases where there is a false-positive screening for PAD.

This research complements some findings from Calabria *et al*. 2018 [277]. That study examined the absolute cardiovascular risk of 2,820 Indigenous Australians using the Australian NVDPA algorithm. In that analysis, 16% of participants aged 35 to 74 years of age were classified as a high primary five-year risk of a major adverse cardiovascular event. The author acknowledged that there is a deficiency in how younger Indigenous Australians are being risk-stratified using these conventional models. One study examined the calibration and discrimination of the Framingham equation in 1,448 Indigenous people living in remote communities in Far North Queensland. The Framingham equation underestimated the five-year risk of cardiovascular disease by approximately one third [278]. The NVDPA algorithm does not apply to individuals below the age of 35, and therefore, it could miss people with premature atherosclerotic cardiovascular disease. Cardiovascular-related mortality affects Indigenous people of age 35 to 44 years by approximately 9 to 12 times more than non-Indigenous Australians [145, 281]. The national guidelines recommend a risk-stratified approach to hypertension and dyslipidaemia [143], and new strategies are imperative to identify and treat young Indigenous Australians.

Several caveats should be noted regarding this retrospective and observational analysis. HotH was a community-based study with limited sample size. Therefore, it may not accurately reflect Indigenous populations living in urban and remote areas across Australia. Longitudinal data would be required to evaluate cardiovascular outcomes and to validate some clinical implications. An abnormal ABI differs from symptomatic PAD. Although PAD can be silent, an ABI should be interpreted with other clinical information, such as limb signs and symptoms, which were not documented. Some treatments for PAD, such as aspirin, do not have proven efficacy in the setting of asymptomatic disease [282]. ABI screening was performed on a random leg, thereby reducing sensitivity for the overall detection of PAD. Notwithstanding,

this study raises many questions that are relevant to the health disparities in Indigenous Australians, which are challenging to ascertain fully.

8.5. Conclusions

A considerable portion of Indigenous participants screened had evidence of PAD. Many conventional risk factors were not significantly associated with non-normal ABI. Framingham-based risk algorithms appeared to underestimate the cardiovascular risk of these people. These results raise the possibility that undiagnosed PAD is contributing to health disparities in Indigenous Australians. If larger studies were to confirm these findings, the argument for incorporating ABI screening into national practice guidelines would be very compelling.

CHAPTER 9: UTILITY OF $CHADS_2$-BASED SCORES FOR PREDICTING CARDIOVASCULAR OUTCOMES FOLLOWING PAD AND OTHER VASCULAR PRESENTATIONS

ABSTRACT

Background: Prior studies have demonstrated a high incidence of major adverse cardiovascular events (MACE) in people with peripheral artery disease (PAD). The question remains whether all patients with PAD should be treated with the most intensive therapies, or if there is a role for a risk-stratified approach akin to atrial fibrillation management.

Objectives: To evaluate several $CHADS_2$-based scores ($CHADS_2$, CHA_2DS_2-VASc, R_2CHADS_2) for predicting MACE in PAD following hospital presentations, compared with clinical manifestations of other vascular territories.

Methods: Data were obtained from patient presentations to metropolitan Emergency Departments in South Australia, between June 2012 and July 2016. An analysis was performed on the period of observation following an acute presentation with PAD (n=2,371), coronary artery disease (CAD, n=25,253), and cerebrovascular accident (CVA, n=11,151), until a subsequent occurrence of MACE (composite of myocardial infarction, stroke, and mortality), or the end of the follow-up. $CHADS_2$-based scores were calculated for these presentations, and discrimination of these risk prediction models was evaluated.

Results: For presentations with a $CHADS_2$ score of 0 and ≥4, the incidence of subsequent MACE (per 100 person-years) increased from 27.1 to 120.1 for PAD, 14.2 to 73.4 for CVA, and 4.0 to 69.3 for CAD, respectively. The risk of MACE for every additional $CHADS_2$ point was higher for CAD (hazard ratio [HR] 2.00, 95% CI, 1.95 to 2.05, $p<0.01$), compared with CVA (HR 1.53, 95% CI, 1.40 to 1.57, $p<0.01$) and PAD (HR 1.45, 95% CI, 1.38 to 1.53, $p<0.01$). When comparing the different models for PAD, there was higher hazard ratio for a unit change in the $CHADS_2$ score (HR 1.45, 95% CI, 1.38 to 1.53, $p<0.01$), compared with CHA_2DS_2-VASc (HR 1.32, 95% CI, 1.27 to 1.38, $p<0.01$), and R_2CHADS_2 (HR 1.30, 95% CI, 1.25 to 1.35, $p<0.01$). The C-statistic for the $CHADS_2$ score predicting MACE was lower in

PAD, (C-statistic 0.53, 95% CI, 0.51 to 0.56, p=0.01), compared with CVA (C-statistic 0.59, 95% CI, 0.58 to 0.60, p<0.01) and CAD (C-statistic 0.64, 95% CI, 0.63 to 0.65, p<0.01). The R_2CHADS_2 score was the best predictor of MACE in CAD (C-statistic 0.67, 95% CI, 0.66 to 0.68, p<0.01).

Conclusions: The incidence of subsequent MACE was markedly higher following a presentation with PAD, compared with CAD. The $CHADS_2$ risk scores were more predictive of MACE in the CAD setting than for PAD. This highlights the exceptionally high clinical risk in presentations with PAD and suggests that further risk stratification would not be advantageous.

9.1. Introduction

The prescription of any medical therapy requires an individualised consideration for the possible benefit and the risk of harm. For example, in atrial fibrillation (AF), oral anticoagulation significantly reduces the risk of ischemic stroke, while increasing the incidence of major bleeding [283]. The $CHADS_2$ score (congestive heart failure, hypertension, diabetes mellitus, age ≥75 years, prior stroke or transient ischemic attack) is a well-validated and straight-forward risk stratification tool used to guide anticoagulation in AF [284]. Newer scores have incorporated other risk factors, such as renal impairment (R_2CHADS_2) [285], and female sex, age 65-74, and history of vascular disease (CHA_2DS_2-VASc). Anticoagulation is recommended in AF patients that have a medium to high risk of stroke, as at this threshold, the net benefit largely outweighs the risk and harm of major bleeding [283]. The $CHADS_2$ scores can also predict adverse outcomes in other cardiovascular conditions. In coronary artery disease (CAD), a higher $CHADS_2$ score has been associated with more severe lesions [286], and an increased risk of major adverse cardiovascular events (MACE) [287, 288]. However, while these predictive models may discriminate between higher and lower-risk presentations, there is a point where the absolute number of events is too high for this to be clinically relevant [289].

Peripheral artery disease (PAD) is increasingly recognised as a high-risk condition that is linked to MACE and mortality [10, 28, 147]. Many contemporary studies have investigated the efficacy of medical therapies in PAD [63, 107], with evidence of the potential for high modifiable risk reduction [93]. The implementation of more intensive antithrombotic, antihypertensives, anti-inflammatory, lipid-lowering, and glycemia-lowering medications all have a risk/reward trade-off [135, 147]. For instance, in the PAD subset of the COMPASS trial, combined rivaroxaban and aspirin was associated with a 31% relative risk reduction in MACE and 61% relative increase in major bleeding, in comparison with aspirin monotherapy. The benefit of combined rivaroxaban and aspirin was predominantly attributable to a 1% absolute

risk reduction in stroke (and in major adverse limb events), although this was comparable to the absolute increase in major bleeding [31, 63]. There is no consensus regarding the use of combined rivaroxaban and aspirin in PAD. Similarly, the incorporation of intensive targeting of blood pressure, lipid, glucose, and inflammation needs clarification [135, 147].

In people with AF, PAD is associated with a worse prognosis [290], and this would score an additional point when the CHA_2DS_2-VASc is applied [283]. The use of the $CHADS_2$ scores in PAD as a measure of vascular risk has not been determined. Hence, the question remains whether all patients with PAD should be treated with combined rivaroxaban and aspirin, and intensive blood pressure, lipid, glycemia, and inflammatory targets, or whether there is a role for a risk-stratified approach akin to AF management. There are more accurate predictors of mortality and MACE in acute coronary syndrome populations, such as the GRACE and TIMI scores [288, 291]. However, the $CHADS_2$ score is well-known, easy to use, and widely applicable to heterogeneous patient groups. This study examined the predictive value of several $CHADS_2$-based scores in PAD following hospital presentations and compared this with other atherosclerotic disease clinically manifest in other vascular territories.

9.2. Methods

9.2.1. *Data source and study populations*

The study population was drawn retrospectively from a state-wide clinical, administrative, and pathology reporting system assimilated dataset of all patient presentations to metropolitan Emergency Departments in South Australia, between June 2012 and July 2016. Each episode of care was linked to primary and secondary diagnostic codes based on the International Classification of Diseases, version 10, Australia Modified (ICD-10 AM). Patients aged ≥18 years with lower limb PAD (ICD-10 AM codes 170.20-170.24, 173.9, 174.3, 174.5), coronary

artery disease, and cerebrovascular accident as a primary diagnosis were included for analysis. The dataset comprised of patient demographics, diagnoses, medical comorbidities, renal function, troponin, and outcomes related to subsequent hospital presentations and mortality. The analysis was performed on the period of observation following an acute presentation with PAD (n = 2,371), coronary artery disease (n = 25,253), and cerebrovascular accident (n = 11,151) until a subsequent representation with MACE or the end of the follow-up period. Presentations, where there was missing data during the initial encounter, were excluded from the study sample. The research proposal was approved by the Southern Adelaide Clinical Human Research Ethics Committee (EC00188).

9.2.2. Study aims

The primary outcome of interest was hospital representation with MACE, defined as a composite of non-fatal myocardial infarction, non-fatal cerebrovascular accident, and cardiovascular-related mortality. The secondary outcome of interest was all-cause mortality. The period of observation was from the initial encounter until a representation with MACE, death, or the end of the follow-up period (July 2017).

This analysis aimed to (1) identify factors associated with MACE and mortality after different vascular presentations, and (2) evaluate the discrimination of $CHADS_2$-based scores for MACE following different vascular presentations.

9.2.3. Calculation of scores

The $CHADS_2$ score was calculated by assigning 1 point for a history of heart failure, hypertension, age ≥75 years, and diabetes mellitus; 2 points for a history of transient ischemic

attack or stroke. The R_2CHADS_2 score added 2 points for renal dysfunction (defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2). The estimated glomerular filtration ratio was calculated using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation [292]. The CHA_2DS_2-VASc was calculated by adding 1 point for heart failure, hypertension, age 65-74, diabetes, and vascular disease history; 2 points for age ≥75 years and history of transient ischemic attack or stroke.

9.2.4. Statistical analysis

Cox proportional hazard regression models were used to identify the factors associated with the primary endpoint in the different vascular presentations. The associations were reported as hazard ratios (HR) with a 95% confidence interval, with $p < 0.05$ considered as statistically significant. The Cox proportional hazard regression model was used to examine the relative increase in the hazard ratio of the primary outcome for each additional point of the $CHADS_2$ scores. The incidence rate per 100 patient-years of the primary outcome was calculated for different vascular presentations according to the $CHADS_2$ score. The discriminatory ability of the CHADS2 scores was evaluated with the C-statistic, where a value of less than or equal to 0.5 was considered ineffective and a value above 0.7, suggesting acceptable discrimination [293]. All analyses used STATA 15.1 (StataCorp, College Station, TX).

9.3. Results

9.3.1. Factors associated with MACE

The factors associated with MACE in all vascular presentations were age (years, hazard ratio [HR] 1.03, 95% CI 1.03 to 1.04, p<0.01), female sex (HR 1.06, 95% CI, 1.01 to 1.11, p=0.02),

CVA compared to CAD (HR 2.04, 95% CI, 1.94 to 2.15, p<0.01), PAD compared to CAD (HR 3.05, 95% CI, 2.81 to 3.30, p<0.01), prior vascular disease of one territory (HR 1.69, 95% CI, 1.59 to 1.79, p<0.01), two territories (HR 2.80, 95% CI 2.49 to 3.14, p<0.01) and three territories (HR 4.17, 95% CI, 2.47 to 7.07, p<0.01) (Table 9.1).

For PAD presentations, cancer (HR 1.76, 95% CI, 1.10 to 2.82, p=0.02), hypertension (HR 1.75, 95% CI, 1.05 to 2.90, p=0.03), prior vascular disease in one territory (HR 3.11, 95% CI, 1.20 to 8.10, p=0.02), two territories (HR 7.72, 95% CI, 1.25 to 47.61, p=0.03), and three vascular territories (HR 13.94, 95% CI, 1.27 to 153.36, p=0.03), were predictive of MACE (Table 9.2).

Table 9.1: Factors associated with MACE in all presentations

Characteristic	MACE			
	HR	95% CI	95% CI	p value
Age (years)	1.03	1.03	1.04	<0.01
Gender (female)	1.06	1.01	1.11	0.02
Vascular presentation				
CAD presentation	Ref.			
CVA presentation	2.04	1.94	2.15	<0.01
PAD presentation	3.05	2.81	3.30	<0.01
Renal impairment	0.99	0.99	0.99	<0.01
Past history				
1 vascular territory	1.69	1.59	1.79	<0.01
2 vascular territories	2.80	2.49	3.14	<0.01
3 vascular territories	4.17	2.47	7.07	<0.01

95% CI, 95% confidence interval; CAD, coronary artery disease; CVA, cerebrovascular disease; PAD, peripheral artery disease; HR, hazard ratio

Table 9.2: Factors associated with MACE in PAD presentations

Characteristic	MACE			
	HR	95% CI	95% CI	p value
Age (years)	1.02	1.00	1.04	0.07
Gender (female)	0.97	0.65	1.46	0.88
Renal impairment	0.99	0.98	1.00	0.03
Troponin rise	1.00	1.00	1.00	0.62
Past history				
1 vascular territory	3.11	1.20	8.10	0.02
2 vascular territories	7.72	1.25	47.61	0.03
3 vascular territories	13.94	1.27	153.36	0.03
Atrial fibrillation	1.00	0.60	1.67	0.99
Myocardial infarction	0.64	0.22	1.81	0.40
PAD	0.55	0.22	1.39	0.21
Chronic obstructive airways disease	0.70	0.15	3.31	0.65
Obesity	1.42	0.57	3.52	0.45
Cancer	1.76	1.10	2.82	0.02
Diabetes mellitus	1.29	0.78	2.13	0.33
Hypertension	1.75	1.05	2.90	0.03
Heart failure	1.18	0.75	1.85	0.47
Coronary artery bypass graft	0.75	0.35	1.61	0.47
Percutaneous coronary intervention	0.42	0.17	1.05	0.06

9.3.2. Factors associated with all-cause mortality

The factors associated with all-cause mortality in all vascular presentations were age (years, HR 1.06, 95% CI 1.06 to 1.07, p<0.01), female sex (HR 1.13, 95% CI, 1.06 to 1.21, p<0.01), CVA compared to CAD (HR 3.07, 95% CI, 2.85 to 3.30, p<0.01), PAD compared to CAD (HR 1.66, 95% CI, 1.42 to 1.94, p<0.01), prior vascular disease of one territory (HR 1.41, 95% CI, 1.30 to 1.54, p<0.01), two territories (HR 2.13, 95% CI 1.77 to 2.56, p<0.01) and three territories (HR 3.04, 95% CI, 1.36 to 6.78, p=0.01) (Table 9.3).

For PAD presentations, age (years, HR 1.03, 95% CI, 1.00 to 1.07, p=0.05), and cancer (HR 2.34, 95% CI, 1.21 to 4.52, p=0.01) were significantly predictive of all cause-mortality.

Renal impairment was marginally associated with less mortality (HR 0.98, 95% CI, 0.97 to 0.99, p<0.01) (Table 9.4).

Table 9.3: Factors associated with mortality in all presentations

Characteristic	Mortality			
	HR	95% CI	95% CI	p value
Age (years)	1.06	1.06	1.07	<0.01
Gender (female)	1.13	1.06	1.21	<0.01
Vascular group				
CAD presentation	Ref.			
CVA presentation	3.07	2.85	3.30	<0.01
PAD presentation	1.66	1.42	1.94	<0.01
Renal impairment	0.98	0.98	0.99	<0.01
Past history				
1 vascular territory	1.41	1.30	1.54	<0.01
2 vascular territories	2.13	1.77	2.56	<0.01
3 vascular territories	3.04	1.36	6.78	0.01

Table 9.4: Factors associated with mortality in PAD presentations

Characteristic	Mortality			
	HR	95% CI	95% CI	p value
Age (years)	1.03	1.99	1.07	0.05
Gender (female)	1.10	0.62	1.96	0.74
Renal impairment	0.98	0.97	0.99	<0.01
Troponin rise	1.00	1.00	1.00	0.90
Past history				
1 vascular territory	1.38	0.26	7.40	0.71
2 vascular territories	2.26	0.96	53.2	0.61
3 vascular territories	9.19	0.23	363.4	0.24
Atrial fibrillation	1.07	0.52	2.18	0.86
Myocardial infarction	1.73	0.31	9.74	0.53
PAD	1.10	0.22	5.51	0.91
Chronic obstructive airways disease	0.37	0.03	3.84	0.40
Obesity	2.09	0.48	9.08	0.33
Cancer	2.34	1.21	4.52	0.01
Diabetes mellitus	1.12	0.53	2.34	0.77
Hypertension	1.93	0.93	4.01	0.08
Heart failure	1.28	0.93	2.35	0.43
Coronary artery bypass graft	0.74	0.25	2.23	0.60
Percutaneous coronary intervention	0.30	0.07	1.25	0.10

9.3.3. Discrimination of MACE using CHADS2-based scores

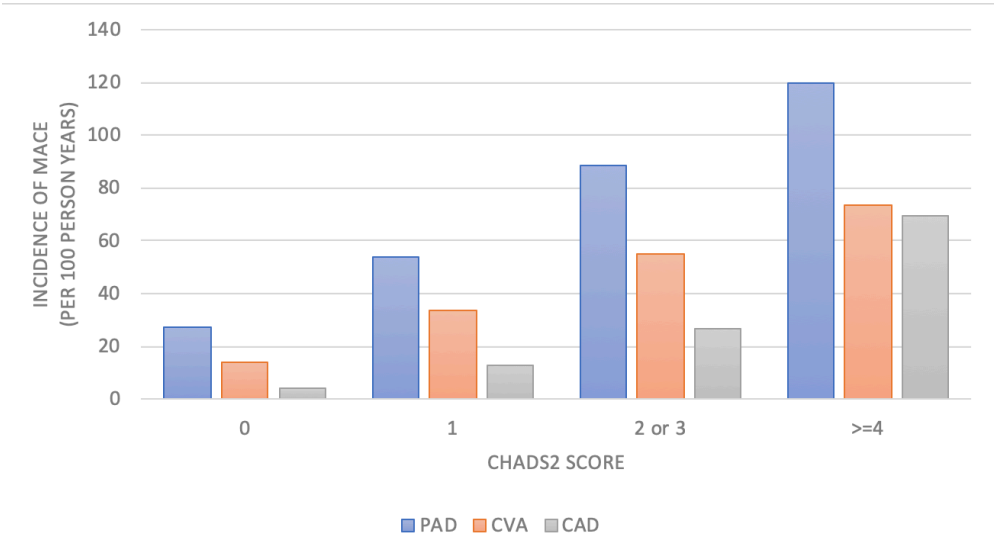
For presentations with a $CHADS_2$ score of 0 and ≥4, the incidence of subsequent MACE (per 100 person-years) increased from 27.1 to 120.1 for PAD, 14.2 to 73.4 for CVA, and 4.0 to 69.3 for CAD, respectively (Figure 9.1).

Table 9.5 outlines the increase in the risk of MACE for each unit change in the $CHADS_2$-based scores. The hazard ratio for every additional $CHADS_2$ point was higher for CAD (HR 2.00, 95% CI, 1.95 to 2.05, p<0.01), compared with CVA (HR 1.53, 95% CI, 1.40 to 1.57, p<0.01) and PAD (HR 1.45, 95% CI, 1.38 to 1.53, p<0.01). When comparing the different models for PAD, there was higher hazard ratio for a unit change in the $CHADS_2$ score

(HR 1.45, 95% CI, 1.38 to 1.53, p<0.01), compared with CHA_2DS_2-VASc (HR 1.32, 95% CI, 1.27 to 1.38, p<0.01), and R_2CHADS_2 (HR 1.30, 95% CI, 1.25 to 1.35, p<0.01).

The C-statistic for the $CHADS_2$ score predicting MACE was lower in PAD, (C-statistic 0.53, 95% CI, 0.51 to 0.56, p=0.01), compared with CVA (C-statistic 0.59, 95% CI, 0.58 to 0.60, p<0.01) and CAD (C-statistic 0.64, 95% CI, 0.63 to 0.65, p<0.01) (Table 9.6). All $CHADS_2$-based models had weak discrimination in PAD and were lower than in CAD. The R_2CHADS_2 score was the best predictor of MACE in CAD (C-statistic 0.67, 95% CI, 0.66 to 0.68, p<0.01).

Figure 9.1: Incidence rates of MACE according to vascular presentation and $CHADS_2$ score



MACE incidence rate (per 100 person-years)	PAD	CVA	CAD
$CHADS_2$ score			
0	27.1	14.2	4.0
1	54.0	33.4	13.0
2 or 3	88.8	55.0	26.8
≥ 4	120.1	73.4	69.3

Table 9.5: Increased risk of MACE by unit change in $CHADS_2$-based scores

	PAD			CVA			CAD		
Score	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
$CHADS_2$	1.45	1.38 – 1.53	<0.01	1.53	1.49 – 1.57	<0.01	2.00	1.95 – 2.05	<0.01
CHA_2DS_2-VASc	1.32	1.27 – 1.38	<0.01	1.41	1.38 – 1.44	<0.01	1.60	1.57 – 1.63	<0.01
R_2CHADS_2	1.30	1.25 – 1.35	<0.01	1.38	1.35 – 1.40	<0.01	1.69	1.66 – 1.72	<0.01

Table 9.6: C-statistics of CHADS2-based scores in predicting MACE, according to vascular presentation

	C-statistic	95% CI	p value
$CHADS_2$ Score			
PAD	0.533	0.510 – 0.557	0.01
CVA	0.593	0.582 – 0.604	<0.01
CAD	0.636	0.626 – 0.646	<0.01
CHA_2DS_2-VASc Score			
PAD	0.547	0.523 – 0.571	0.01
CVA	0.604	0.593 – 0.616	<0.01
CAD	0.627	0.616 – 0.637	<0.01
R_2CHADS_2 Score			
PAD	0.536	0.512 – 0.560	0.01
CVA	0.604	0.593 – 0.615	<0.01
CAD	0.674	0.664 – 0.683	<0.01

9.4. Discussion

This study compared the predictive utility of the $CHADS_2$, R_2CHADS_2, and CHA_2DS_2-VASc scores after presentations with atherosclerotic disease involving different vascular territories, to determine whether prior observations in the coronary circulation could be extended to PAD. The $CHADS_2$ risk scores were more predictive of MACE in CAD setting than for PAD, as these events occurred less frequently. These findings highlighted the precariousness of PAD presentations and suggested that further risk stratification is unnecessary. In this analysis, the discriminative aspect of risk scoring was assessed; that is, the differentiation of high and low-risk presentations. Calibration was not evaluated (i.e., prediction of absolute risk of MACE). Nevertheless, with these high event rates, calibration would not strengthen the case for using $CHADS_2$-based scores in the management of PAD.

The worse outcomes in PAD might be connected to the high clinical complexity of these presentations, and less medical treatment being prescribed. It is expected that these presentations were mostly critical limb ischemia or acute limb ischemia. Treatment of these conditions can be complicated, as patients may require urgent lower limb revascularisation, amputation, wound care, and the management of concomitant illnesses. These types of hospital admissions can be protracted, and patients often require multidisciplinary support [29]. A less intensive approach may be adopted in this setting, than with other acute vascular presentations, due to concerns regarding adverse reactions. Prior observational studies found that PAD patients were less likely to receive optimal risk factor control and guideline-recommended therapies compared with coronary artery disease or cerebrovascular disease [10, 12].

PAD management could change based on recent research [19, 61, 76, 294]. The COMPASS study randomised 6,391 individuals with PAD, to either combined rivaroxaban and aspirin, rivaroxaban alone, or aspirin alone. Combined rivaroxaban and aspirin significantly

reduced the risk of stroke and major adverse limb events, although increasing major bleeding, compared to aspirin alone [31, 63]. The SPRINT trial showed that intensive blood pressure control could reduce the likelihood of MACE, at the expense of other adverse events, when compared to a more conventional approach. While the participants were classified as high risk, many components of the $CHADS_2$ score were criteria for exclusion, including heart failure, age ≥75 years old, diabetes mellitus, and previous stroke [84]. Protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors significantly reduced low-density lipoprotein cholesterol (LDL-C), corresponding with MACE reduction across all studied patients, even those below traditional targets (<1.8 mmol/L or <70 mg/dL) [146]. Likewise, new medical therapies for diabetes and elevated high-sensitivity C-reactive protein can reduce the risk of MACE [122, 295-297]. These studies were designed to demonstrate relative efficacy with a more intensive treatment strategy. However, they do not define the absolute benefit of therapy in the broader population, which could be achieved through risk stratification.

Clinical decisions require a nuanced consideration for potential treatment risks and benefits. A treatment threshold has been described, whereby the benefits of any preventative therapy matches the net harm and costs [289]. For instance, if combined rivaroxaban and aspirin are at the treatment threshold for PAD, a 1% absolute risk reduction in stroke and major adverse limb events would be equivalent to the risk of bleeding, medication, costs, and patient preference to avoid an adverse event. COMPASS evaluated people with a stable history of PAD [31, 63]. Whereas, the PAD presentations in this study were more critical. These were very high-risk conditions that could not be meaningfully risk-stratified with the $CHADS_2$ scores. Theoretically, people presenting to hospital with PAD had more to gain from combined rivaroxaban and aspirin, given such high rates of subsequent MACE. With evidence for pharmacotherapies mostly extrapolated from lower risk cohorts [147], there is no consensus regarding the role of intensive medical therapy in unstable PAD presentations [29]. ATLAS

ACS-2-TIMI-51 examined the efficacy of adding low-dose rivaroxaban to antiplatelets in patients with recent acute coronary syndrome [298]. More evidence for the management of critical limb ischemia is required, in the same way that acute coronary syndrome is researched [29]. While the benefit of combined rivaroxaban and aspirin might be assumed in critical limb ischemia, further validation is necessary. There could be a high bleeding risk, as patients with critical limb ischemia potentially require several procedures. The relative benefits and risks of combined rivaroxaban and aspirin might not be consistent across the entire PAD population.

The $CHADS_2$ score was predictive of MACE in the CAD setting, which is consistent with previous studies [286-288]. For CAD presentations with a $CHADS_2$ score of 0 and ≥4, the observed incidence of MACE (per 100 person-years) was 4.03 and 69.3, respectively. Seemingly, even the lowest risk CAD presentations would be deserving of more intensive treatment. However, some preventative therapies, such as PCSK9 inhibitors, are yet to be introduced entirely. Some caveats include a lack of long-term safety and efficacy data, as well as economic considerations. The European Society of Cardiology stated the cost-effectiveness of PCSK9 inhibitor treatment at different LDL-C levels, which focused on the cost per quality of life years gained. They recommended PCSK9 inhibitors for the highest risk individuals, where LDL-C reduction would be most pronounced [94]. Therefore, there could be greater value in implementing new medications in CAD with $CHADS_2$ ≥4, (or R_2CHADS_2 ≥4) and with all PAD presentations, compared with lower risk presentations.

CVA was associated with a moderate risk of MACE, somewhere between that for CAD and PAD. In the period of observation following CVA, there was an approximately 3-fold increase in mortality compared with CAD. The C-statistics suggest that the $CHADS_2$-based scores were reasonable predictors of MACE for CVA. In the lowest risk-stratified CVA presentation ($CHADS_2$ score 0), the incidence of MACE was comparable to CAD with

$CHADS_2$ score 1. Nevertheless, the usefulness of the $CHADS_2$ scores in CVA would depend on the therapeutic threshold for implementing a different management strategy. The risks of harm associated with antithrombotic and antihypertensive therapy in acute stroke can differ significantly from other conditions [299]. Cardiovascular outcome studies typically make a distinction of investigating stable cerebrovascular disease, as in COMPASS, where a recent stroke (less than one month) was excluded [64].

The $CHADS_2$ score is useful in AF because the absolute risk of stroke is low, and each component of the score is influential [300]. In this study, a Cox multivariate regression analysis was performed on risk factors of MACE in PAD. Of the components of the $CHADS_2$ score, age, heart failure, and diabetes mellitus were not clearly associated with MACE. Only hypertension and prior cancer were associated with an increased risk of MACE. Therefore, the incidence of MACE in PAD was invariably high, and conventional risk factors were not strongly predictive of recurrent events. These findings reveal how the $CHADS_2$ scores were broadly lacking, and they were unlikely to improve substantially if new risk factors were added.

The ideal risk model would be simple, accurate, and widely applicable to different vascular populations and discriminate those who should and should not receive treatment. There are other validated risk scores with good discriminatory power in acute coronary syndrome [288, 291]. The $CHADS_2$ score is easy to calculate and widely used for AF. Previous studies have found the score to be applicable to both stable and unstable coronary artery disease presentations [286, 301, 302]. This type of algorithm can be applied retrospectively to cardiovascular outcome studies, such as COMPASS. The goal would be to identify groups at high risk of ischemic events, without an equivalent increase in the risk of adverse events, such as major bleeding.

In this study, $CHADS_2$-based scores were tested in predicting a composite of MACE endpoints. The elevated MACE rates observed in PAD were mostly attributable to non-fatal stroke and myocardial infarction. In AF, the focus of treatment is in preventing ischaemic stroke. Whereas, in PAD, there are separate risks of major adverse limb events, myocardial infarction, and mortality. The impact of preventative treatment can vary for each outcome. If an algorithm were used to guide the management of PAD, it would need to have adequate discrimination for predicting these individual outcomes. In the PAD subgroup of COMPASS, combined rivaroxaban and aspirin was associated with a relative risk reduction in MACE, ischaemic stroke, and major adverse limb events, but not for myocardial infarction or mortality [63]. A meta-analysis combined the randomised controlled trials of intensive blood pressure control. A lower blood pressure target was associated with a significant relative risk reduction in MACE and stroke, a borderline significant reduction in myocardial infarction, and no observed reduction in mortality [303]. PCSK9 inhibitors lowered the likelihood of MACE, principally through lesser myocardial infarction and stroke [93]. In the PAD subgroup treated with empagliflozin, there was an observed risk reduction in MACE predominantly from lower mortality and hospitalisation for heart failure [107]. Therefore, algorithm-based management of PAD would need to be relevant to all major adverse events.

When devising an algorithm, the dynamic nature of risk should be considered. In this analysis, $CHADS_2$-based scores were applied to hospital presentations in order to predict subsequent MACE. There was a relatively short period of observation for PAD, irrespective of the baseline $CHADS_2$ score. As this period of observation lengthens, there is more potential for the score to increase. In AF, the delta $CHADS_2$ score (increase in the score between baseline and follow-up), has been shown to predict stroke risk [304]. This was highlighted in a study where 90% of AF patients without baseline comorbidities developed at least one new risk factor before an ischaemic stroke occurred [305].

An individual's residual risk is highly dependent on the management they receive. The $CHADS_2$-based scores evaluate non-modifiable risk factors, such as age, gender, and medical history. Notwithstanding, the clinical course of diabetes, hypertension, and stroke can be altered, using medical and lifestyle interventions, without affecting the $CHADS_2$ score. An ideal algorithm would incorporate risk factor control, as a continuous variable, and could be applied for a dynamic perspective of residual risk. The difficulty with incorporating continuous variables is that they cannot be applied to all studies. A simplified approach would be to focus on the prescription of medications. For instance, antihypertensive or diabetic medication use would add modifiability to $CHADS_2$-based algorithms. The HAS-BLED score was developed for risk-stratifying bleeding risk in AF patients [306]. A high score is not necessarily a deterrent for prescribing anticoagulation. Instead, it provides a dynamic clinician assessment of bleeding risk, with the possibility for modifiability [307].

Several caveats should be noted concerning this observational and retrospective analysis. It involved an administrative dataset, which examined a large heterogeneous population that presented to the emergency department. Given the real-world dataset, it permits the opportunity to study many individuals, reflecting contemporary practice to a higher degree than the restrictive and controlled cohorts enrolled in clinical trials. However, such data is limited in the information obtained, including patient complexity and the use of procedures and medical therapies. Such data can be subject to inaccuracies and potential coding errors. While multivariate regression analysis was performed, the possibility of unmeasured confounding cannot be excluded.

9.5. Conclusions

The $CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_2 scores had weak discrimination for MACE that commonly occurred following acute presentations with PAD. New strategies and medical therapies are required to improve outcomes in PAD, and there was minimal evidence that further risk stratification would be advantageous.

CHAPTER 10: CONCLUSIONS AND FUTURE DIRECTIONS

10.1. Research overview and aims

This thesis evaluated associations between clinical factors and cardiovascular mortality and morbidity in PAD, which provides new insights into the management of these patients. The framework for this research was to draw comparisons between groups to understand outcome discrepancies. There are numerous reasons for the disproportionately higher rates of MACE and mortality in PAD, compared with atherosclerosis clinically manifested in other territories. The breadth of this problem is too extensive to discuss here in its entirety. One aspect that was outside of the scope of this research was the impact of health care systems at the population-level.

The introductory chapter reviewed the magnitude of the problem and the evidence for treatments recommended by the professional bodies. This thesis tackled gaps in the understanding of intensive risk factor control; gender differences in cardiovascular events; lower limb revascularisation outcomes; dyslipidaemia disorders that associate with PAD; the prevalence of PAD in Australia; and the clinical utility of risk scores.

10.2. Individual study findings

We summarise the individual study findings below while recognising the limitations of these post hoc observational analyses.

Chapter 2 examined the impact of intensive individual and multiple risk factor control on cardiovascular outcomes in ACCELERATE.

- PAD patients had a greater incidence of MACE (17.0% vs 13.3%, p<0.001), and all-cause mortality (8.2% vs 3.6%, p<0.001), when compared with coronary artery disease (CAD)-only.
- Higher MACE rates for PAD were observed even in the setting of an HbA1c <7.0% (12.8% vs 10.7%, p=0.02), LDL-C <70mg/dL (15.7% vs 11.4%, p<0.001), systolic BP <130 mmHg (13.8% vs 11.0%, p=0.01), diastolic BP <80 mmHg (15.9% vs 12.0%, p<0.001), triglycerides <150 mg/dL (14.1% vs 11.9%, p=0.02), non-smoking (15.6% vs 12.3%, p<0.001), and multiple risk factor control (14.0% vs 11.1%, p=0.004), in comparison with CAD-only.
- For PAD patients that achieved optimal glycaemia, LDL-C, systolic BP, diastolic BP, triglycerides, BMI, and smoking abstinence, individually or in combination, there was no significant relative risk reduction in MACE.
- Optimal hs-CRP levels were the lone risk factor that correlated with improved cardiovascular outcomes (HR 0.78, 95% CI, 0.61 to 0.99, p=0.05).
- These findings highlight the challenges with altering the natural history of PAD and indicate a need for new strategies, including inflammatory control.

Chapter 3 examined for differences in coronary artery plaque burden and progression in PAD and non-PAD patients, according to risk factor control.

- PAD patients had a smaller external elastic membrane volume, but comparable percent atheroma volume, compared to non-PAD patients. This could indicate a proclivity for negative remodelling in the coronary circulation. We propose that negative remodelling is also occurring in the peripheries and is clinically manifested by early ischaemia.

- Both PAD and non-PAD groups had a comparable annualised change in percent atheroma volume and the number of people classified as having plaque progression and regression. We postulate that the underlying cardiovascular risk profile can explain differences in plaque observed in other studies.
- Combined risk factor control and optimal triglycerides were associated with greater total atheroma volume regression in non-PAD patients, compared to the PAD group.
- In PAD patients achieving individual or combined risk factor control, there was no significant difference in percent atheroma volume or total atheroma volume change, compared with PAD individuals that did not. This suggests resilience to medical treatments and is consistent with the clinical observations in chapter two.

Chapter 4 was a systematic review and meta-analysis that combined 14 studies reporting a multivariate-adjusted hazard ratio for gender differences in mortality or MACE.

- Male gender was associated with a greater risk of all-cause mortality (HR 1.13, 95% CI 1.10 to 1.16, $p<0.001$) and MACE (HR 1.10, 95% CI 1.06 to 1.14, $p<0.001$).
- Higher mortality and MACE rates in men with PAD occurred despite other accepted gender disparities. This divergence was potentially more significant in advanced diseases, such as critical limb ischaemia or when a lower extremity procedure was performed.
- These results might represent how females benefitted from treatment.

Chapter 5 compared MACE and mortality rates of PAD patients in ACCELERATE, according to gender.

- The rates of MACE in females and males were comparable (16.0% vs 17.4%, p=0.32, respectively). Females were significantly less likely to die from any cause than males (5.6% vs 9.2%, p=0.01).
- Male gender was independently predictive of all-cause mortality (adjusted hazard ratio [HR] 1.62, 95% CI, 1.11 to 2.38, p=0.01).
- Female PAD patients that achieved more optimal risk factor control had significantly lower all-cause mortality than their male counterparts (4.0% vs 8.6%, p=0.004).
- Given the disconnect between mortality and non-fatal MACE, major adverse limb events might contribute to the observed gender differences.
- We postulate that women with PAD benefit more from intensive risk factor control than men, through a reduction in major adverse limb events.

In chapter 6, propensity-score matched analysis was performed to compare long-term (up to 8 years) outcomes of endovascular and surgical lower extremity revascularisation.

- The incidence of complications was as followed: major adverse limb events ([MALE], 17.9% and 15.3%, p<0.0001), all-cause mortality (29.3% and 29.1%, p=0.89), all-cause mortality or MALE (40.4% and 38.3%, p<0.0001), in unmatched surgery and endovascular patients, respectively.
- With a propensity-matched comparison, endovascular repair had a higher rate of all-cause mortality (HR 1.14, 95% CI 1.10 to 1.19, p<0.001), composite of all-cause mortality or MALE (HR 1.12, 95% CI, 1.07 to 1.16, p<0.001), and composite of other limb events (HR 1.12, 95 % CI, 1.09 to 1.15, p<0.001), but similar rates of MALE, major bleeding, all-cause acute rehospitalisations, compared to surgery. Endovascular patients were less likely to require urgent surgical reintervention (HR 0.70, 95% CI,

0.63 to 0.78, p<0.001), elective surgical reintervention (HR 0.65, 95% CI, 0.60 to 0.69, p<0.001), or experience arterial embolus/ thrombus (HR 0.83, 95% CI, 0.76 to 0.91, p<0.001), but at the expense of higher urgent endovascular reintervention (HR 1.18, 95 % CI, 1.09 to 1.28, p<0.001), elective endovascular intervention (HR 1.49, 95% CI, 1.42 to 1.56, p<0.001), and minor amputation (HR 1.35, 95% CI, 1.24 to 1.47, p<0.001).

- Male gender was associated with an 8% higher rate of mortality or MALE.
- Some cardiovascular conditions appeared to be protective, such as a prior percutaneous coronary intervention or coronary artery bypass graft operation. This could indicate an advantage from completed coronary revascularisation when this precedes PAD revascularisation.
- The high rates of major adverse events emphasise the dangers of revascularisation, and some less critical cases might be better managed conservatively.
- There were many associations between non-PAD comorbidities and MALE or mortality, indicating that there are multiple mechanisms likely contributing. Patients have complex multidisciplinary needs that continued beyond the revascularisation procedure.

Chapter 7 was an exploratory analysis of the Heart of the Heart study. The Indigenous participants underwent a clinical assessment that included an ankle-brachial index (ABI) and an extensive lipid panel.

- People with abnormal ABI had a lower median total HDL-mediated cholesterol efflux capacity, compared to normal ABI (30.6% [27.3, 34.2] and 31.1% [29.5, 34.2], p=0.02). There was a significantly lower adjusted total HDL-mediated cholesterol efflux

capacity (adjusted difference -1.40%, 95% CI, -2.46 to -0.24, p=0.02) and ABCA-1 cholesterol efflux capacity (adjusted difference -1.20%, 95% CI, -2.11 to -0.19, p=0.02), when comparing abnormal with normal ABI.

- This result has potential mechanistic implications underscoring a role for dysfunctional HDL in the pathogenesis of PAD.
-

Chapter 8 evaluated the usefulness of ABI screening for the Heart of the Heart participants.

- Of 185 Indigenous participants, 58% had normal, 28% abnormal, and 15% borderline ABI, from a single lower limb screened.
- When applying the National Vascular Disease Prevention Alliance algorithm to non-normal ABI, the proportion of people that were very low, low, moderate and high risk was 53%, 16%, 8% and 23%, respectively. This indicates that cardiovascular risk was being grossly underestimated in most affected individuals.
- These findings suggest that undiagnosed PAD could be contributing to health disparities in Indigenous Australians.

In chapter 9, several $CHADS_2$-based scores ($CHADS_2$, CHA_2DS_2-VASc, R_2CHADS_2) were evaluated for predicting MACE after PAD-related hospital presentations, compared with other hospital presentations.

- For presentations with a $CHADS_2$ score of 0 and ≥4, the incidence of subsequent MACE (per 100 person-years) increased from 27.1 to 120.1 for PAD, 14.2 to 73.4 for cerebrovascular accident (CVA), and 4.0 to 69.3 for CAD, respectively.

- The risk of MACE for every additional $CHADS_2$ point was higher for CAD (hazard ratio [HR] 2.00, 95% CI, 1.95 to 2.05, p<0.01), compared with PAD (HR 1.45, 95% CI, 1.38 to 1.53, p<0.01).
- The C-statistic for the $CHADS_2$ score predicting MACE was lower in PAD, (C-statistic 0.53, 95% CI, 0.51 to 0.56, p=0.01), compared with CVA (C-statistic 0.59, 95% CI, 0.58 to 0.60, p<0.01) and CAD (C-statistic 0.64, 95% CI, 0.63 to 0.65, p<0.01).
- These results demonstrated the exceptionally high clinical risk of presentations with PAD and that further risk stratification did not appear advantageous.

10.3. Overarching conclusions

Important caveats should be noted regarding these observational and retrospective analyses. Some chapters utilised administrative data, which had the potential for coding and data entry inaccuracies. Each study had a varying degree of clinical information, and therefore, the group comparisons that were made could have been affected by confounding. We formulate the following hypotheses regarding PAD, in contrast to other high-risk conditions, such as coronary artery disease; although, these require further clarification through randomised and prospective studies.

- PAD patients have a distinct clinical phenotype, relating to functional status, cardiovascular risk factors and other medical comorbidities. This high medical complexity is a major contributor to cardiovascular mortality and morbidity.
- The risks and benefits of intensively treating PAD are different, and this partly explains the low prescription of proven therapies in observational studies.
- Concomitant coronary artery atheroma in PAD patients have specific properties that are more resilient to the effects of preventative treatments.

- PAD-affected women are less likely to experience major adverse limb events and mortality, and this is linked to lower utilisation of lower extremity revascularisation and a more beneficial impact of preventative treatments.
- Major adverse limb events are an additional driver of cardiovascular and non-cardiovascular mortality.
- There are some enduring advantages of surgical revascularisation, including less all-cause mortality and endovascular reintervention, compared to an initial endovascular approach.
- Dysfunctional HDL cholesterol is associated with the pathogenesis of PAD and can be a therapeutic target.
- Undiagnosed PAD is contributing to health disparities in Indigenous Australians
- PAD-related hospital presentations are invariably high-risk, whereby evaluation using a clinical risk score is not advantageous.

10.4. Clinical implications and future directions

10.4.1. Clinical implications

The high medical complexity of PAD patients requires multidisciplinary management. As was evident from the Steno-2 study, a team approach is the most effective means of delivering risk factor modification, and in monitoring for adverse reactions. In chapter 2 and 3, there was no convincing benefit from intensive multiple risk factor control, although this data had limitations. Further investigation through randomised controlled trials would better characterise the effects of multiple risk factor control in PAD. These studies do not negate the importance of intensive risk factor control, but they do provide perspective regarding the challenges in altering the natural history of this condition. Chapter 9 considered the treatment

threshold for prescribing preventative therapies. For example, the risks and benefits of the intensive management of dyslipidaemia are distinct from hyperglycaemia. There are differences in toxicity, dependent on the medications used and patient-specific factors, thus necessitating an individualised decision that is less reliant on broad-based recommendations.

Other preventative treatments need to be implemented, such as combined antithrombotics and new strategies for inflammatory control. Chapter 7 showed a link between lower HDL-medicated cholesterol efflux capacity and early PAD, and this is another potential target for therapeutic modification. A subgroup analysis of PAD in clinical trials of HDL mimetics would be of interest.

The importance of clinical discretion was again evident in chapter 6, where all PAD patients had a high risk of mortality and major adverse limb events (MALE), irrespective of the revascularisation strategy performed. Peripheral artery revascularisation is sometimes the only possible option to resolve lifestyle-limiting claudication. In this setting, the long-term risk of mortality, MALE and other limb events need to be weighed against this benefit. There were many observed links between non-PAD comorbidities and MALE or mortality, and these conditions require management from various healthcare specialists.

PAD exists across a clinical spectrum, ranging from asymptomatic disease, intermittent claudication, and critical limb-threatening ischaemia that requires lower limb revascularisation or amputation. Most of the evidence for pharmacotherapies have been extrapolated from lower risk cohorts. Chapter 9 highlighted the precarious nature of PAD-related hospital presentations, and these types of patients are rarely included in clinical trials. These conditions could not be meaningfully risk-stratified with the $CHADS_2$ scores. Theoretically, people presenting to hospital with PAD have more to gain from preventative treatments. While the benefit of intensive therapies, such as combined rivaroxaban and aspirin, might be assumed, further

validation is necessary. More evidence for the management of critical limb ischemia is required, in the same way, that acute coronary syndrome is researched. Chapter 8 looked beyond the management of established disease at the benefits of screening for early PAD. ABI is a simple and non-invasive test with good sensitivity and specificity for detection of asymptomatic disease. The role of ABI screening of Indigenous Australians needs further clarification, as this could help address the accepted problem of cardiovascular risk underestimation in this population.

Chapter 4, 5 and 6 identified significant gender disparities. Acknowledging there are different interactions between risk factors and PAD, according to gender, the impact of preventative treatments might differ also. While contemporary clinical trials have investigated the effects of medical treatment in preventing major adverse limb events, fewer women are usually enrolled. We postulate that women with PAD benefit more from intensive risk factor control than men. Research into the effects of intensive risk factor control in PAD, with a gender-specific lens, is indicated. An appreciation for these issues could inspire more effective health initiatives that are attentive to both gender groups. There may be a role for PAD care delivery models that focus separately on men and women, as has been introduced in other aspects of cardiovascular medicine.

10.4.2. Ankle-brachial index screening

The Heart of the Heart study raised serious questions about the under-diagnosis of Indigenous populations living in Central Australia. Current national guidelines do not endorse the use of ankle-brachial index screening for asymptomatic people. Local research is required into the prevalence of PAD across different populations in Australia. A more extensive study in different Australian regions is required. As with Heart of the Heart, detailed clinical

information and blood tests should be collected to assess Framingham risk scores and to evaluate how an abnormal ABI could resultantly alter management. A longitudinal study, where participants are followed for years, would help validate some inferences made about the association between an abnormal ankle-brachial index and cardiovascular risk.

10.4.3. Multifactorial intervention clinical trial

This research featured observational studies of patient cohorts and administrative datasets. The possibilities for new treatment strategies were discussed that need evaluation in a clinical trial. We would propose a randomised controlled trial of PAD patients that investigates new approaches to care. A central question is the safety, efficacy, and viability of intensive multiple risk factor control. The Steno-2 study demonstrated the cardiovascular benefits of multifactorial intervention in a 160-patient randomised controlled trial of diabetes patients that occurred for 7.8 years [134]. Steno-2 provides a framework for powering a study of multiple risk factor control. However, risk factor targets should be based on contemporary ideas, and lifestyle modification needs to be tailored towards the challenges of PAD. Some cardiovascular targets include systolic blood pressure <130 mmHg, diastolic blood pressure <80 mmHg, triglycerides <150 mg/dL, high-sensitivity C-reactive protein <2.0 mg/L, body mass index <25 kg/m^2, and glycated haemoglobin <7.0%. Some functional goals include treadmill walking distance and quality of life.

The types of initiatives that could be incorporated include:

- Specialist physician and nursing consultation for the initiation and titration of preventative medical therapies

- Routine evaluation of cardiovascular risk factors with patient feedback in the form of personalised counselling, progress charts, letters and mobile phone messages
- Regular treadmill walking program supervised by an exercise physiologist
- Dietician-led weight loss consultation that includes consistent phone and email-based communication centred around the recording of a food journal
- Motivational interviewing and behavioural psychology strategies that encourage self-directed goals regarding walking, weight, and risk factors
- Use of smartphones to monitor walking steps
- Group-based education and support, in clinics and through social media platforms
- Pharmacy counselling and review focused on medication compliance and minimisation of errors

The efficacy of multifactorial intervention can be assessed through serial measurements of walking, quality of life, risk factor control, exploratory laboratory tests, and the incidence of adverse events. The outcomes of interest include:

- Walking distance (maximum walking distance and claudication-onset walking distance) using a validated treadmill protocol [308]
- Quality of life and pain scores using a validated questionnaire [309]
- Total number of controlled risk factors
- Ankle-brachial index
- Inflammatory and lipid risk markers, including high-sensitivity C-reactive protein and cholesterol efflux capacity
- Incidence of MACE, hospitalisation, major adverse limb events and other serious adverse events

A clinical trial of PAD patients designed to test hypotheses generated from this body of work could create a road map for the future.

REFERENCES

1. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet.* 2013;382(9901):1329-40.
2. Song P, Rudan R, Zhu Y, Fowkes F, Rahimi K, Fowkes F, et al. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis - The Lancet Global Health. *Lancet Glob Health.* 2019;7(8):e1020-30.
3. Aronow WS. Peripheral arterial disease of the lower extremities. Arch Med Sci. 82012. p. 375-88.
4. McDermott MM. Lower extremity manifestations of peripheral artery disease: the pathophysiologic and functional implications of leg ischemia. *Circ Res.* 2015;116(9):1540-50.
5. McDermott MM, Guralnik JM, Ferrucci L, Tian L, Liu K, Liao Y, et al. Asymptomatic Peripheral Arterial Disease Is Associated With More Adverse Lower Extremity Characteristics Than Intermittent Claudication. *Circulation.* 2008.
6. Dua A, Lee CJ. Epidemiology of Peripheral Arterial Disease and Critical Limb Ischemia. *Tech Vasc Interv Radiol.* 2016;19(2):91-5.
7. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg.* 2007;45 Suppl S:S5-67.
8. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *Jama.* 2001;286(11):1317-24.
9. Stoffers HE, Rinkens PE, Kester AD, Kaiser V, Knottnerus JA. The prevalence of asymptomatic and unrecognized peripheral arterial occlusive disease. *Int J Epidemiol.* 1996;25(2):282-90.
10. Cacoub PP, Abola MT, Baumgartner I, Bhatt DL, Creager MA, Liau CS, et al. Cardiovascular risk factor control and outcomes in peripheral artery disease patients in the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Atherosclerosis.* 2009;204(2):e86-92.
11. Armstrong EJ, Chen DC, Westin GG, Singh S, McCoach CE, Bang H, et al. Adherence to guideline-recommended therapy is associated with decreased major adverse cardiovascular events and major adverse limb events among patients with peripheral arterial disease. *J Am Heart Assoc.* 2014;3(2):e000697.

12. Berger JS, Ladapo JA. Underuse of Prevention and Lifestyle Counseling in Patients With Peripheral Artery Disease. *J Am Coll Cardiol.* 2017;69(18):2293-300.
13. McDermott MM, Hahn EA, Greenland P, Cella D, Ockene JK, Brogan D, et al. Atherosclerotic risk factor reduction in peripheral arterial diseasea: results of a national physician survey. *J Gen Intern Med.* 2002;17(12):895-904.
14. Hirsch AT, Murphy TP, Lovell MB, Twillman G, Treat-Jacobson D, Harwood EM, et al. Gaps in public knowledge of peripheral arterial disease: the first national PAD public awareness survey. *Circulation.* 2007;116(18):2086-94.
15. Aday AW, Lawler PR, Cook NR, Ridker PM, Mora S, Pradhan AD. Lipoprotein Particle Profiles, Standard Lipids, and Peripheral Artery Disease Incidence. *Circulation.* 2018;138(21):2330-41.
16. Joshi PH, Martin SS. Unraveling the Risk of Peripheral Artery Disease. *Circulation.* 2018;138(21):2342-4.
17. Price JF, Mowbray PI, Lee AJ, Rumley A, Lowe GD, Fowkes FG. Relationship between smoking and cardiovascular risk factors in the development of peripheral arterial disease and coronary artery disease: Edinburgh Artery Study. *Eur Heart J.* 1999;20(5):344-53.
18. McDermott MM, Greenland P, Liu K, Guralnik JM, Criqui MH, Dolan NC, et al. Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. *Jama.* 2001;286(13):1599-606.
19. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease. *Circulation.* 2016;135(12).
20. Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *Jama.* 2008;300(2):197-208.
21. Gu X, Man C, Zhang H, Fan Y. High ankle-brachial index and risk of cardiovascular or all-cause mortality: A meta-analysis. *Atherosclerosis.* 2019;282:29-36.
22. Resnick HE, Lindsay RS, McDermott MM, Devereux RB, Jones KL, Fabsitz RR, et al. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: the Strong Heart Study. *Circulation.* 2004;109(6):733-9.
23. Miura T, Minamisawa M, Ueki Y, Abe N, Nishimura H, Hashizume N, et al. Impressive predictive value of ankle-brachial index for very long-term outcomes in patients with cardiovascular disease: IMPACT-ABI study. *PLoS One.* 2017;12(6):e0177609.

24. Kumakura H, Kanai H, Hojo Y, Iwasaki T, Ichikawa S. Long-term survival and fate of the leg in de novo intermittent claudication. *Eur Heart J Qual Care Clin Outcomes.* 2017;3(3):208-15.

25. Bonaca MP, Gutierrez JA, Creager MA, Scirica BM, Olin J, Murphy SA, et al. Acute Limb Ischemia and Outcomes With Vorapaxar in Patients With Peripheral Artery Disease: Results From the Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients With Atherosclerosis-Thrombolysis in Myocardial Infarction 50 (TRA2 degrees P-TIMI 50). *Circulation.* 2016;133(10):997-1005.

26. Sigvant B, Kragsterman B, Falkenberg M, Hasvold P, Johansson S, Thuresson M, et al. Contemporary cardiovascular risk and secondary preventive drug treatment patterns in peripheral artery disease patients undergoing revascularization. *J Vasc Surg.* 2016;64(4):1009-17.e3.

27. Wiseman JT, Fernandes-Taylor S, Saha S, Havlena J, Rathouz PJ, Smith MA, et al. Endovascular Versus Open Revascularization for Peripheral Arterial Disease. *Ann Surg.* 2017;265(2):424-30.

28. Hess CN, Rogers RK, Wang TY, Fu R, Gundrum J, Allen LaPointe NM, et al. Major Adverse Limb Events and 1-Year Outcomes After Peripheral Artery Revascularization. *J Am Coll Cardiol.* 2018;72(9):999-1011.

29. Armstrong EJ, Alam S, Henao S, Lee AC, DeRubertis BG, Montero-Baker M, et al. Multidisciplinary Care for Critical Limb Ischemia: Current Gaps and Opportunities for Improvement. *J Endovasc Ther.* 2019;26(2):199-212.

30. Jones WS, Patel MR, Dai D, Vemulapalli S, Subherwal S, Stafford J, et al. High mortality risks after major lower extremity amputation in Medicare patients with peripheral artery disease. *Am Heart J.* 2013;165(5):809-15, 15.e1.

31. Anand SS, Caron F, Eikelboom JW, Bosch J, Dyal L, Aboyans V, et al. Major Adverse Limb Events in Lower Extremity Peripheral Artery Disease: COMPASS Trial. *J Am Coll Cardiol.* 2018;71:2306-15.

32. Willigendael EM, Teijink JA, Bartelink ML, Kuiken BW, Boiten J, Moll FL, et al. Influence of smoking on incidence and prevalence of peripheral arterial disease. *J Vasc Surg.* 2004;40(6):1158-65.

33. Armstrong EJ, Wu J, Singh GD, Dawson DL, Pevec WC, Amsterdam EA, et al. Smoking cessation is associated with decreased mortality and improved amputation-free

survival among patients with symptomatic peripheral artery disease. *J Vasc Surg.* 2014;60(6):1565-71.

34. Selvarajah S, Black JH, 3rd, Malas MB, Lum YW, Propper BW, Abularrage CJ. Preoperative smoking is associated with early graft failure after infrainguinal bypass surgery. *J Vasc Surg.* 2014;59(5):1308-14.

35. Quick CR, Cotton LT. The measured effect of stopping smoking on intermittent claudication. *Br J Surg.* 1982;69 Suppl:S24-6.

36. Hennrikus D, Joseph AM, Lando HA, Duval S, Ukestad L, Kodl M, et al. Effectiveness of a smoking cessation program for peripheral artery disease patients: a randomized controlled trial. *J Am Coll Cardiol.* 2010;56(25):2105-12.

37. Tonstad S, Farsang C, Klaene G, Lewis K, Manolis A, Perruchoud AP, et al. Bupropion SR for smoking cessation in smokers with cardiovascular disease: a multicentre, randomised study. *Eur Heart J.* 2003;24(10):946-55.

38. Rigotti NA, Pipe AL, Benowitz NL, Arteaga C, Garza D, Tonstad S. Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: a randomized trial. *Circulation.* 2010;121(2):221-9.

39. Rigotti NA, Regan S, Levy DE, Japuntich S, Chang Y, Park ER, et al. Sustained care intervention and postdischarge smoking cessation among hospitalized adults: a randomized clinical trial. *Jama.* 2014;312(7):719-28.

40. Stead LF, Perera R, Bullen C, Mant D, Hartmann-Boyce J, Cahill K, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev.* 2012(11).

41. Chang P, Nead KT, Olin JW, Myers J, Cooke JP, Leeper NJ. Effect of physical activity assessment on prognostication for peripheral artery disease and mortality. *Mayo Clin Proc.* 2015;90(3):339-45.

42. Fakhry F, van de Luijtgaarden KM, Bax L, den Hoed PT, Hunink MG, Rouwet EV, et al. Supervised walking therapy in patients with intermittent claudication. *J Vasc Surg.* 2012;56(4):1132-42.

43. Fokkenrood HJ, Bendermacher BL, Lauret GJ, Willigendael EM, Prins MH, Teijink JA. Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. *Cochrane Database Syst Rev.* 2013(8):Cd005263.

44. Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER, 3rd, Cohen DJ, Reynolds MR, et al. Supervised exercise, stent revascularization, or medical therapy for claudication due to

aortoiliac peripheral artery disease: the CLEVER study. *J Am Coll Cardiol.* 2015;65(10):999-1009.

45. Meneses AL, Ritti-Dias RM, Parmenter B, Golledge J, Askew CD. Combined Lower Limb Revascularisation and Supervised Exercise Training for Patients with Peripheral Arterial Disease: A Systematic Review of Randomised Controlled Trials. *Sports Med.* 2016;47(5).

46. Gommans LN, Fokkenrood HJ, van Dalen HC, Scheltinga MR, Teijink JA, Peters RJ. Safety of supervised exercise therapy in patients with intermittent claudication. *J Vasc Surg.* 2015;61(2):512-8.e2.

47. De La Haye R, Diehm C, Blume J, Breddin K, Gerlach H, Rettig K, et al. [An epidemiologic study of the value and limits of physical therapy/exercise therapy in Fontaine stage II arterial occlusive disease]. *Vasa Suppl.* 1992;38:1-40.

48. Lauret GJ, Fakhry F, Fokkenrood HJ, Hunink MG, Teijink JA, Spronk S. Modes of exercise training for intermittent claudication. *Cochrane Database Syst Rev.* 2014(7):Cd009638.

49. Mays RJ, Regensteiner JG. Therapy for Peripheral Artery Disease: Gaps in Treating Patients With Claudication. *Circulation.* 2014;130(12):929-31.

50. Gardner AW, Parker DE, Montgomery PS, Blevins SM. Step-monitored home exercise improves ambulation, vascular function, and inflammation in symptomatic patients with peripheral artery disease: a randomized controlled trial. *J Am Heart Assoc.* 2014;3(5):e001107.

51. Berger JS, Krantz MJ, Kittelson JM, Hiatt WR. Aspirin for the prevention of cardiovascular events in patients with peripheral artery disease: a meta-analysis of randomized trials. *JAMA.* 2009;301(18):1909-19.

52. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet.* 1996;348(9038):1329-39.

53. Cacoub PP, Bhatt DL, Steg PG, Topol EJ, Creager MA. Patients with peripheral arterial disease in the CHARISMA trial. *Eur Heart J.* 2009;30(2):192-201.

54. Strobl FF, Brechtel K, Schmehl J, Zeller T, Reiser MF, Claussen CD, et al. Twelve-month results of a randomized trial comparing mono with dual antiplatelet therapy in endovascularly treated patients with peripheral artery disease. *J Endovasc Ther.* 2013;20(5):699-706.

55. Belch JJ, Dormandy J, Biasi GM, Cairols M, Diehm C, Eikelboom B, et al. Results of the randomized, placebo-controlled clopidogrel and acetylsalicylic acid in bypass surgery for peripheral arterial disease (CASPAR) trial. *J Vasc Surg.* 2010;52(4):825-33, 33.e1-2.

56. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. *N Engl J Med.* 2010.

57. Hiatt WR, Fowkes FGR, Heizer G, Berger JS, Baumgartner I, Held P, et al. Ticagrelor versus Clopidogrel in Symptomatic Peripheral Artery Disease. *N Engl J Med.* 2017;376(1):32-40.

58. Cosmi B, Conti E, Coccheri S. Anticoagulants (heparin, low molecular weight heparin and oral anticoagulants) for intermittent claudication. *Cochrane Database Syst Rev.* 2014(5):Cd001999.

59. The Warfarin Antiplatelet Vascular Evaluation Trial Investigators. Oral Anticoagulant and Antiplatelet Therapy and Peripheral Arterial Disease. *N Engl J Med.* 2007;357(3).

60. Dutch Bypass Oral anticoagulants or Aspirin (BOA) Study Group. Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery (The Dutch Bypass Oral Anticoagulants or Aspirin Study): a randomised trial. *Lancet.* 2000;355(9201):346-51.

61. Task Force Members, Aboyans V, Ricco JB, Bartelink MEL, Bjorck M, Brodmann M, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg.* 2017.

62. Mega JL, Braunwald E, Wiviott SD, Bassand J-P, Bhatt DL, Bode C, et al. Rivaroxaban in Patients with a Recent Acute Coronary Syndrome. *N Engl J Med.* 2012.

63. Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet.* 2017;391:219-29.

64. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. *N Engl J Med.* 2017.

65. Tangelder MJ, Nwachuku CE, Jaff M, Baumgartner I, Duggal A, Adams G, et al. A review of antithrombotic therapy and the rationale and design of the randomized edoxaban in patients with peripheral artery disease (ePAD) trial adding edoxaban or clopidogrel to aspirin after femoropopliteal endovascular intervention. *J Endovasc Ther.* 2015;22(2):261-8.

66. ClinicalTrials.gov [Internet]. National Library of Medicine (US)- Identifier NCT02504216. Efficacy and Safety of Rivaroxaban in Reducing the Risk of Major Thrombotic Vascular Events in Subjects With Symptomatic Peripheral Artery Disease Undergoing Peripheral Revascularization Procedures of the Lower Extremities (VOYAGER PAD) 2018 [July 21, 2015]. Available from: https://clinicaltrials.gov/ct2/show/NCT02504216.

67. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *Jama.* 2003;289(19):2560-72.

68. Sundstrom J, Arima H, Woodward M, Jackson R, Karmali K, Lloyd-Jones D, et al. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. *Lancet.* 2014;384(9943):591-8.

69. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an Angiotensin-Converting–Enzyme Inhibitor, Ramipril, on Cardiovascular Events in High-Risk Patients. *N Engl J Med.* 2009;342(3).

70. The ONTARGET Investigators. Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events. *N Engl J Med.* 2008;358(15).

71. Shahin Y, Barnes R, Barakat H, Chetter IC. Meta-analysis of angiotensin converting enzyme inhibitors effect on walking ability and ankle brachial pressure index in patients with intermittent claudication. *Atherosclerosis.* 2013;231(2):283-90.

72. Paravastu SC, Mendonca DA, Da Silva A. Beta blockers for peripheral arterial disease. *Cochrane Database Syst Rev.* 2013(9):Cd005508.

73. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Himmelfarb CD, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. *Hypertension.* 2017.

74. Mui K-W, Sleeswijk M, Hout Hvd, Baal Jv, Navis G, Woittiez A-J. Incidental Renal Artery Stenosis Is an Independent Predictor of Mortality in Patients with Peripheral Vascular Disease. *Jasn.* 2006.

75. Aronow WS, Fleg JL, Pepine CJ, Artinian NT, Bakris G, Brown AS, et al. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus documents developed in collaboration with the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology, American Society of Hypertension,

American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension. *J Am Coll Cardiol.* 2011;57(20):2037-114.

76. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Himmelfarb CD, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. *Hypertension.* 2017;71(6).

77. National Heart Foundation of Australia, "Guideline for the diagnosis and management of hypertension in adults". *National Heart Foundation of Australia.* 2016.

78. Hoare E, Kingwell BA, Jennings GLR. Blood Pressure Down Under, but Down Under What? US and Australian Hypertension Guideline Conversation. *Hypertension.* 2018;71(6):972-5.

79. Bakris G, Ali W, Parati G. ACC/AHA Versus ESC/ESH on Hypertension Guidelines: JACC Guideline Comparison. *J Am Coll Cardiol.* 2019;73(23):3018-26.

80. Nerenberg KA, Zarnke KB, Leung AA, Dasgupta K, Butalia S, McBrien K, et al. Hypertension Canada's 2018 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults and Children. *Can J Cardiol.* 2018;34(5):506-25.

81. Smith SC, Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, et al. AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update. *Circulation.* 2011;124(22).

82. The ACCORD Study Group. Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus. *N Engl J Med.* 2010;362(17).

83. Reboldi G, Gentile G, Angeli F, Ambrosio G, Mancia G, Verdecchia P. Effects of intensive blood pressure reduction on myocardial infarction and stroke in diabetes: a meta-analysis in 73,913 patients. *J Hypertens.* 2011;29(7):1253-69.

84. The SPRINT Research Group. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med.* 2015;373(22).

85. Ferri C, Ferri L, Desideri G. Management of Hypertension in the Elderly and Frail Elderly. *High Blood Press Cardiovasc Prev.* 2017;24(1):1-11.

86. Heart Protection Study Collaborative Group. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. *J Vasc Surg.* 2007;45(4):645-54; discussion 53-4.

87. Kumbhani DJ, Steg PG, Cannon CP, Eagle KA, Smith SC, Jr., Goto S, et al. Statin therapy and long-term adverse limb outcomes in patients with peripheral artery disease: insights from the REACH registry. *Eur Heart J.* 2014;35(41):2864-72.

88. Cholesterol Treatment Trialists Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet.* 2010;376(9753):1670-81.

89. Foley TR, Singh GD, Kokkinidis DG, Choy HK, Pham T, Amsterdam EA, et al. High-Intensity Statin Therapy Is Associated With Improved Survival in Patients With Peripheral Artery Disease. *J Am Heart Assoc.* 2017;6(7).

90. Aronow WS, Nayak D, Woodworth S, Ahn C. Effect of simvastatin versus placebo on treadmill exercise time until the onset of intermittent claudication in older patients with peripheral arterial disease at six months and at one year after treatment. *Am J Cardiol.* 2003;92(6):711-2.

91. Mondillo S, Ballo P, Barbati R, Guerrini F, Ammaturo T, Agricola E, et al. Effects of simvastatin on walking performance and symptoms of intermittent claudication in hypercholesterolemic patients with peripheral vascular disease. *Am J Med.* 2003;114(5):359-64.

92. Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Daly DD, DePalma SM, et al. 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. *J Am Coll Cardiol.* 2017;70(14).

93. Bonaca MP, Nault P, Giugliano RP, Keech AC, Pineda AL, Kanevsky E, et al. Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease: Insights From the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk). *Circulation.* 2018;137(4):338-50.

94. Landmesser U, Chapman MJ, Farnier M, Gencer B, Gielen S, Hovingh GK, et al. European Society of Cardiology/European Atherosclerosis Society Task Force consensus statement on proprotein convertase subtilisin/kexin type 9 inhibitors: practical guidance for use in patients at very high cardiovascular risk. *Eur Heart J.* 2017;38(29):2245-55.

95. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet.* 2010;375(9733):2215-22.

96. Adler AI, Stevens RJ, Neil A, Stratton IM, Boulton AJ, Holman RR. UKPDS 59: hyperglycemia and other potentially modifiable risk factors for peripheral vascular disease in type 2 diabetes. *Diabetes Care.* 2002;25(5):894-9.

97. American Diabetes Association. Peripheral arterial disease in people with diabetes. *Diabetes Care.* 2003;26(12):3333-41.

98. Singh S, Armstrong EJ, Sherif W, Alvandi B, Westin GG, Singh GD, et al. Association of elevated fasting glucose with lower patency and increased major adverse limb events among patients with diabetes undergoing infrapopliteal balloon angioplasty. *Vasc Med.* 2014;19(4):307-14.

99. Takahara M, Kaneto H, Iida O, Gorogawa S, Katakami N, Matsuoka TA, et al. The influence of glycemic control on the prognosis of Japanese patients undergoing percutaneous transluminal angioplasty for critical limb ischemia. *Diabetes Care.* 2010;33(12):2538-42.

100. Low Wang CC, Blomster JI, Heizer G, Berger JS, Baumgartner I, Fowkes FGR, et al. Cardiovascular and Limb Outcomes in Patients With Diabetes and Peripheral Artery Disease: The EUCLID Trial. *J Am Coll Cardiol.* 2018;72(25):3274-84.

101. Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers JP, Duckworth WC, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia.* 2009;52(11):2288-98.

102. Zoungas S, Arima H, Gerstein HC, Holman RR, Woodward M, Reaven P, et al. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. *Lancet Diabetes Endocrinol.* 2017;5(6):431-7.

103. Sinclair A, Morley JE, Rodriguez-Manas L, Paolisso G, Bayer T, Zeyfang A, et al. Diabetes mellitus in older people: position statement on behalf of the International Association of Gerontology and Geriatrics (IAGG), the European Diabetes Working Party for Older People (EDWPOP), and the International Task Force of Experts in Diabetes. *J Am Med Dir Assoc.* 2012;13(6):497-502.

104. Alsahli M, Gerich JE. Hypoglycemia in Patients with Diabetes and Renal Disease. J Clin Med. 42015. p. 948-64.

105. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med.* 2017;377(7):644-57.

106. Verma S, Mazer CD, Al-Omran M, Inzucchi SE, Fitchett D, Hehnke U, et al. Cardiovascular Outcomes and Safety of Empagliflozin in Patients With Type 2 Diabetes Mellitus and Peripheral Artery Disease: A Subanalysis of EMPA-REG OUTCOME. *Circulation.* 2017.

107. Verma S, Mazer CD, Al-Omran M, Inzucchi SE, Fitchett D, Hehnke U, et al. Cardiovascular Outcomes and Safety of Empagliflozin in Patients With Type 2 Diabetes Mellitus and Peripheral Artery Disease: A Subanalysis of EMPA-REG OUTCOME. *Circulation.* 2018;137(4):405-7.

108. Reinecke H, Unrath M, Freisinger E, Bunzemeier H, Meyborg M, Luders F, et al. Peripheral arterial disease and critical limb ischaemia: still poor outcomes and lack of guideline adherence. *Eur Heart J.* 2015;36(15):932-8.

109. Abu Dabrh AM, Steffen MW, Undavalli C, Asi N, Wang Z, Elamin MB, et al. The natural history of untreated severe or critical limb ischemia. *J Vasc Surg.* 2015;62(6):1642-51.e3.

110. Chung J, Modrall JG, Ahn C, Lavery LA, Valentine RJ. Multidisciplinary care improves amputation-free survival in patients with chronic critical limb ischemia. *J Vasc Surg.* 2015;61(1):162-9.

111. van Aalst FM, Verwijmeren L, van Dongen EPA, de Vries JPM, de Groot E, Noordzij PG. Frailty and functional outcomes after open and endovascular procedures for patients with peripheral arterial disease: A systematic review. *J Vasc Surg.* 2019.

112. Koch M, Trapp R, Kulas W, Grabensee B. Critical limb ischaemia as a main cause of death in patients with end-stage renal disease: a single-centre study. *Nephrol Dial Transplant.* 2004;19(10):2547-52.

113. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation.* 2014;129(25 Suppl 2):S102-38.

114. Cronin O, Morris DR, Walker PJ, Golledge J. The association of obesity with cardiovascular events in patients with peripheral artery disease. *Atherosclerosis.* 2013;228(2):316-23.

115. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *J Am Coll Cardiol.* 2009;53(21):1925-32.

116. Galal W, van Gestel Y, Hoeks SE, Sin DD, Winkel TA, Bax JJ, et al. The obesity paradox in patients with peripheral arterial disease. *Chest.* 2008;134(5):925-30.
117. Terzikhan N, Lahousse L, Verhamme KM, Franco OH, Ikram AM, Stricker BH, et al. COPD is associated with an increased risk of peripheral artery disease and mortality. ERJ Open Res. 42018.
118. Mani P, Department of Cardiovascular Medicine CC, Cleveland, Ohio, Puri R, Department of Cardiovascular Medicine CC, Cleveland, Ohio, Cleveland Clinic Coordinating Center for Clinical Research CC, Cleveland, Ohio, Schwartz GG, et al. Association of Initial and Serial C-Reactive Protein Levels With Adverse Cardiovascular Events and Death After Acute Coronary Syndrome: A Secondary Analysis of the VISTA-16 Trial. *JAMA Cardiol.* 2019;4(4):314-20.
119. Carrero JJ, Andersson Franko M, Obergfell A, Gabrielsen A, Jernberg T. hsCRP Level and the Risk of Death or Recurrent Cardiovascular Events in Patients With Myocardial Infarction: a Healthcare-Based Study. *J Am Heart Assoc.* 2019;8(11):e012638.
120. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM, Jr., Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med.* 2008;359(21):2195-207.
121. Best Endovascular vs. Best Surgical Therapy in Patients With Critical Limb Ischemia [Internet]. [cited 16 Nov 2019]. Available from: https://clinicaltrials.gov/ct2/show/NCT02060630.
122. Ridker PM, MacFadyen JG, Everett BM, Libby P, Thuren T, Glynn RJ. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. *Lancet.* 2018;391(10118):319-28.
123. Rader DJ, Hovingh GK. HDL and cardiovascular disease. *Lancet.* 2014;384(9943):618-25.
124. Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. *Jama.* 2001;285(19):2481-5.
125. Pradhan AD, Shrivastava S, Cook NR, Rifai N, Creager MA, Ridker PM. Symptomatic peripheral arterial disease in women: nontraditional biomarkers of elevated risk. *Circulation.* 2008;117(6):823-31.

126. Tall AR, Rader DJ. Trials and Tribulations of CETP Inhibitors. *Circ Res.* 2018;122(1):106-12.

127. Nicholls SJ, Nelson AJ. HDL and cardiovascular disease. *Pathology.* 2019;51(2):142-7.

128. Rohatgi A, Khera A, Berry JD, Givens EG, Ayers CR, Wedin KE, et al. HDL Cholesterol Efflux Capacity and Incident Cardiovascular Events. *N Engl J Med.* 2014.

129. Guerin M, Silvain J, Gall J, Darabi M, Berthet M, Frisdal E, et al. Association of Serum Cholesterol Efflux Capacity With Mortality in Patients With ST-Segment Elevation Myocardial Infarction. *J Am Coll Cardiol.* 2018;72(25):3259-69.

130. Gibson CM, Korjian S, Tricoci P, Daaboul Y, Yee M, Jain P, et al. Safety and Tolerability of CSL112, a Reconstituted, Infusible, Plasma-Derived Apolipoprotein A-I, After Acute Myocardial Infarction. 2016.

131. Study to Investigate CSL112 in Subjects With Acute Coronary Syndrome (AEGIS-II) [Internet]. 2018 [cited 17 Aug 2019]. Available from: https://clinicaltrials.gov/ct2/show/NCT03473223.

132. Gæde P, Lund-Andersen H, Parving H-H, Pedersen O. Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes. *N Engl J Med.* 2008.

133. Gaede P, Oellgaard J, Carstensen B, Rossing P, Lund-Andersen H, Parving HH, et al. Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial. *Diabetologia.* 2016;59(11):2298-307.

134. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med.* 2003;348(5):383-93.

135. Ridker PM. Clinician's Guide to Reducing Inflammation to Reduce Atherothrombotic Risk: JACC Review Topic of the Week. *J Am Coll Cardiol.* 2018;72(25):3320-31.

136. Attar R, Wester A, Koul S, Eggert S, Andell P. Peripheral artery disease and outcomes in patients with acute myocardial infarction. 2019.

137. Grenon SM, Vittinghoff E, Owens CD, Conte MS, Whooley M, Cohen BE. Peripheral artery disease and risk of cardiovascular events in patients with coronary artery disease: insights from the Heart and Soul Study. *Vasc Med.* 2013;18(4):176-84.

138. Subherwal S, Bhatt DL, Li S, Wang TY, Thomas L, Alexander KP, et al. Polyvascular disease and long-term cardiovascular outcomes in older patients with non-ST-segment-elevation myocardial infarction. *Circ Cardiovasc Qual Outcomes.* 2012;5(4):541-9.

139. Kendir C, van den Akker M, Vos R, Metsemakers J. Cardiovascular disease patients have increased risk for comorbidity: A cross-sectional study in the Netherlands. *Eur J Gen Pract.* 2018;24(1):45-50.

140. Hirsch AT, Allison MA, Gomes AS, Corriere MA, Duval S, Ershow AG, et al. A call to action: women and peripheral artery disease: a scientific statement from the American Heart Association. *Circulation.* 2012;125(11):1449-72.

141. McDermott MM, Greenland P, Liu K, Criqui MH, Guralnik JM, Celic L, et al. Sex differences in peripheral arterial disease: leg symptoms and physical functioning. *J Am Geriatr Soc.* 2003;51(2):222-8.

142. Dreyer RP, van Zitteren M, Beltrame JF, Fitridge R, Denollet J, Vriens PW, et al. Gender differences in health status and adverse outcomes among patients with peripheral arterial disease. *J Am Heart Assoc.* 2014;4(1):e000863.

143. National Vascular Disease Prevention Alliance. Guidelines for the management of absolute cardiovascular disease risk. 2012.

144. The Royal Australian College of General Practitioners. Guidelines for preventive activities in general practice. 9th edn. East Melbourne, Vic: RACGP [Internet]. 2018 [cited 17 Aug 2019]. Available from: https://www.racgp.org.au/download/Documents/Guidelines/Redbook9/17048-Red-Book-9th-Edition.pdf.

145. Brown A. Addressing cardiovascular inequalities among indigenous Australians. *Global Cardiology Science and Practice.* 2012;2012(1).

146. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med.* 2017;376(18).

147. Parvar SL, Fitridge R, Dawson J, Nicholls SJ. Medical and lifestyle management of peripheral arterial disease. *J Vasc Surg.* 2018;68(5):1595-606.

148. Lincoff AM, Nicholls SJ, Riesmeyer JS, Barter PJ, Brewer HB, Fox KAA, et al. Evacetrapib and Cardiovascular Outcomes in High-Risk Vascular Disease. *N Engl J Med.* 2017.

149. Klein-Weigel PF, Gutsche-Petrak B, Wolbergs S, Koning C, Flessenkamper I. Secondary medical prevention in patients with peripheral arterial disease - prescriptions of vascular surgeons and medical doctors (angiologists) in a multidisciplinary vascular centre. *Vasa.* 2010;39(2):145-52.

150. Hoeks SE, Scholte op Reimer WJ, van Gestel YR, Schouten O, Lenzen MJ, Flu WJ, et al. Medication underuse during long-term follow-up in patients with peripheral arterial disease. *Circ Cardiovasc Qual Outcomes.* 2009;2(4):338-43.

151. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N Engl J Med.* 2019;380(1):11-22.

152. Hussein AA, Uno K, Wolski K, Kapadia S, Schoenhagen P, Tuzcu EM, et al. Peripheral arterial disease and progression of coronary atherosclerosis. *J Am Coll Cardiol.* 2011;57(10):1220-5.

153. Nicholls SJ, Hsu A, Wolski K, Hu B, Bayturan O, Lavoie A, et al. Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome. *J Am Coll Cardiol.* 2010;55(21):2399-407.

154. Stewart RAH, Held C, Hadziosmanovic N, Armstrong PW, Cannon CP, Granger CB, et al. Physical Activity and Mortality in Patients With Stable Coronary Heart Disease. *J Am Coll Cardiol.* 2017;70(14):1689-700.

155. Bohula EA, Giugliano RP, Cannon CP, Zhou J, Murphy SA, White JA, et al. Achievement of dual low-density lipoprotein cholesterol and high-sensitivity C-reactive protein targets more frequent with the addition of ezetimibe to simvastatin and associated with better outcomes in IMPROVE-IT. *Circulation.* 2015;132(13):1224-33.

156. Januszek R, Mika P, Konik A, Petriczek T, Nowobilski R, Nizankowski R. Effect of treadmill training on endothelial function and walking abilities in patients with peripheral arterial disease. *J Cardiol.* 2014;64(2):145-51.

157. Fedewa MV, Hathaway ED, Ward-Ritacco CL. Effect of exercise training on C reactive protein: a systematic review and meta-analysis of randomised and non-randomised controlled trials. *Br J Sports Med.* 2017;51(8):670-6.

158. Selvin E, Paynter NP, Erlinger TP. The effect of weight loss on C-reactive protein: a systematic review. *Arch Intern Med.* 2007;167(1):31-9.

159. Schlager O, Hammer A, Giurgea A, Schuhfried O, Fialka-Moser V, Gschwandtner M, et al. Impact of exercise training on inflammation and platelet activation in patients with intermittent claudication. *Swiss Med Wkly.* 2012;142:w13623.

160. Golledge J, Cronin O, Iyer V, Bradshaw B, Moxon JV, Cunningham MA. Body mass index is inversely associated with mortality in patients with peripheral vascular disease. *Atherosclerosis.* 2013;229(2):549-55.

161. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *Atherosclerosis.* 2016;252:207-74.

162. Cao C, Wang R, Wang J, Bunjhoo H, Xu Y, Xiong W. Body Mass Index and Mortality in Chronic Obstructive Pulmonary Disease: A Meta-Analysis. PLoS One. 72012.

163. Zhang X, Liu Y, Zhang F, Li J, Tong N. Legacy Effect of Intensive Blood Glucose Control on Cardiovascular Outcomes in Patients With Type 2 Diabetes and Very High Risk or Secondary Prevention of Cardiovascular Disease: A Meta-analysis of Randomized Controlled Trials. *Clin Ther.* 2018;40(5):776-88.e3.

164. Brevetti G, Piscione F, Schiano V, Galasso G, Scopacasa F, Chiariello M. Concomitant coronary and peripheral arterial disease: relationship between the inflammatory status of the affected limb and the severity of coronary artery disease. *J Vasc Surg.* 2009;49(6):1465-71.

165. Eagle KA, Rihal CS, Foster ED, Mickel MC, Gersh BJ. Long-term survival in patients with coronary artery disease: importance of peripheral vascular disease. The Coronary Artery Surgery Study (CASS) Investigators. *J Am Coll Cardiol.* 1994;23(5):1091-5.

166. Aykan AC, Hatem E, Karabay CY, Gul I, Gokdeniz T, Kalaycioglu E, et al. Complexity of lower extremity peripheral artery disease reflects the complexity of coronary artery disease. *Vascular.* 2015;23(4):366-73.

167. Bryniarski KL, Yamamoto E, Takumi H, Xing L, Zanchin T, Sugiyama T, et al. Differences in coronary plaque characteristics between patients with and those without peripheral arterial disease. *Coron Artery Dis.* 2017;28(8):658-63.

168. Vuruskan E, Saracoglu E, Polat M, Duzen IV. Prediction of coronary artery disease severity in lower extremity artery disease patients: A correlation study of TASC II classification, Syntax and Syntax II scores. *Cardiol J.* 2017;24(5):495-501.

169. Kataoka Y, Shao M, Wolski K, Uno K, Puri R, Tuzcu EM, et al. Multiple risk factor intervention and progression of coronary atherosclerosis in patients with type 2 diabetes mellitus. *Eur J Prev Cardiol.* 2013;20(2):209-17.

170. Hartmann M, Huisman J, Bose D, Jensen LO, Schoenhagen P, Mintz GS, et al. Serial intravascular ultrasound assessment of changes in coronary atherosclerotic plaque dimensions and composition: an update. *Eur J Echocardiogr.* 2011;12(4):313-21.
171. Nicholls SJ, Ballantyne CM, Barter PJ, Chapman MJ, Erbel RM, Libby P, et al. Effect of Two Intensive Statin Regimens on Progression of Coronary Disease. *N Engl J Med.* 2011.
172. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *Jama.* 2006;295(13):1556-65.
173. Nicholls SJ, Puri R, Anderson T, Ballantyne CM, Cho L, Kastelein JJ, et al. Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial. *Jama.* 2016;316(22):2373-84.
174. Ward MR, Pasterkamp G, Yeung AC, Borst C. Arterial remodeling. Mechanisms and clinical implications. *Circulation.* 2000;102(10):1186-91.
175. Higgins JP, Higgins JA. Epidemiology of peripheral arterial disease in women. *J Epidemiol.* 2003;13(1):1-14.
176. Paul N, Vuddanda V, Mujib M, Aronow WS. Advances in our understanding of the influence of gender on patient outcomes with peripheral arterial disease co-occurring with diabetes. *Expert Rev Endocrinol Metab.* 2016;11(3):271-9.
177. Garcia M, Mulvagh SL, Merz CNB, Buring JE, Manson JE. Cardiovascular Disease in Women. *Circ Res.* 2016;118:1273-93.
178. Bucholz EM, Butala NM, Rathore SS, Dreyer RP, Lansky AJ, Krumholz HM. Sex Differences in Long-Term Mortality after Myocardial Infarction: A Systematic Review. *Circulation.* 2014;130:757-67.
179. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *Bmj.* 2009;339: b2700.
180. Abtan J, Bhatt DL, Elbez Y, Sorbets E, Eagle K, Reid CM, et al. Geographic variation and risk factors for systemic and limb ischemic events in patients with symptomatic peripheral artery disease: Insights from the REACH Registry. *Clin Cardiol.* 2017;40(9):710-8.
181. Al-Omran M, Tu JV, Johnston KW, Mamdani MM, Kucey DS. Outcome of revascularization procedures for peripheral arterial occlusive disease in Ontario between 1991 and 1998: a population-based study. *J Vasc Surg.* 2003;38(2):279-88.

182. Budtz-Lilly JW, Petersen CN, Pedersen TF, Eldrup N. Male Sex Associated with Increased Long-term Cardiovascular Mortality after Peripheral Vascular Surgery for Atherosclerosis Despite Optimal Medical Treatment. *Eur J Vasc Endovasc Surg.* 2015;50(6):767-73.

183. Cea Soriano L, Fowkes FGR, Johansson S, Allum AM, Garcia Rodriguez LA. Cardiovascular outcomes for patients with symptomatic peripheral artery disease: A cohort study in The Health Improvement Network (THIN) in the UK. *Eur J Prev Cardiol.* 2017;24(18):1927-37.

184. Duffy RP, Adams JE, Callas PW, Schanzer A, Goodney PP, Ricci MA, et al. The influence of gender on functional outcomes of lower extremity bypass. *J Vasc Surg.* 2014;60(5):1282-90, 90.e1.

185. Freisinger E, Malyar NM, Reinecke H, Unrath M. Low rate of revascularization procedures and poor prognosis particularly in male patients with peripheral artery disease - A propensity score matched analysis. *Int J Cardiol.* 2018;255:188-94.

186. Grootenboer N, Hunink MG, Hoeks S, Hendriks JM, van Sambeek MR, Poldermans D. The impact of gender on prognosis after non-cardiac vascular surgery. *Eur J Vasc Endovasc Surg.* 2011;42(4):510-6.

187. Hussain MA, Lindsay TF, Mamdani M, Wang X, Verma S, Al-Omran M. Sex differences in the outcomes of peripheral arterial disease: a population-based cohort study. *CMAJ Open.* 2016;4(1):E124-31.

188. Mustapha JA, Katzen BT, Neville RF, Lookstein RA, Zeller T, Miller LE, et al. Determinants of Long-Term Outcomes and Costs in the Management of Critical Limb Ischemia: A Population-Based Cohort Study. *J Am Heart Assoc.* 2018;7(16):e009724.

189. Schanzer A, Hevelone N, Owens CD, Beckman JA, Belkin M, Conte MS. Statins are independently associated with reduced mortality in patients undergoing infrainguinal bypass graft surgery for critical limb ischemia. *J Vasc Surg.* 2008;47(4):774-81.

190. Sigvant B, Hasvold P, Kragsterman B, Falkenberg M, Johansson S, Thuresson M, et al. Cardiovascular outcomes in patients with peripheral arterial disease as an initial or subsequent manifestation of atherosclerotic disease: Results from a Swedish nationwide study. *J Vasc Surg.* 2017;66(2):507-14.e1.

191. Turley RS, Mi X, Qualls LG, Vemulapalli S, Peterson ED, Patel MR, et al. The Effect of Clinical Care Location on Clinical Outcomes After Peripheral Vascular Intervention in Medicare Beneficiaries. *J Am Coll Cardiol Intv.* 2017;10(11):1161-71.

192. Vaartjes I, de Borst GJ, Reitsma JB, de Bruin A, Moll FL, Grobbee DE, et al. Long-term survival after initial hospital admission for peripheral arterial disease in the lower extremities. *BMC Cardiovasc Disord.* 2009;9:43.

193. Issa SM, Hoeks SE, Scholte op Reimer WJ, Van Gestel YR, Lenzen MJ, Verhagen HJ, et al. Health-related quality of life predicts long-term survival in patients with peripheral artery disease. *Vasc Med.* 2010;15(3):163-9.

194. Arya S, Lee S, Zahner GJ, Cohen BE, Hiramoto J, Wolkowitz OM, et al. The association of comorbid depression with mortality and amputation in veterans with peripheral artery disease. *J Vasc Surg.* 2018;68:536-45.

195. Regitz-Zagrosek V, Oertelt-Prigione S, Prescott E, Franconi F, Gerdts E, Foryst-Ludwig A, et al. Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes. *Eur Heart J.* 2016;37(1):24-34.

196. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *N Engl J Med.* 2007;356(23):2388-98.

197. Mosca L, Barrett-Connor E, Wenger NK. Sex/Gender Differences in Cardiovascular Disease Prevention. *Circulation.* 2011;124:2145-54.

198. Aquarius AE, Smolderen KG, Hamming JF, De Vries J, Vriens PW, Denollet J. Type D personality and mortality in peripheral arterial disease: a pilot study. *Arch Surg.* 2009;144(8):728-33.

199. Bunte MC, House JA, Spertus JA, Cohen DJ, Marso SP, Safley DM. Association between health status and long-term mortality after percutaneous revascularization of peripheral artery disease. *Catheter Cardiovasc Interv.* 2016;87(6):1149-55.

200. Gardner AW, Montgomery PS, Parker DE. Physical activity is a predictor of all-cause mortality in patients with intermittent claudication. *J Vasc Surg.* 2008;47(1):117-22.

201. Genovese EA, Chaer RA, Taha AG, Marone LK, Avgerinos E, Makaroun MS, et al. Risk Factors for Long-Term Mortality and Amputation after Open and Endovascular Treatment of Acute Limb Ischemia. *Ann Vasc Surg.* 2016;30:82-92.

202. Howard DP, Banerjee A, Fairhead JF, Hands L, Silver LE, Rothwell PM. Population-Based Study of Incidence, Risk Factors, Outcome, and Prognosis of Ischemic Peripheral Arterial Events: Implications for Prevention. *Circulation.* 2015;132(19):1805-15.

203. Jeon-Slaughter H, Tsai S, Kamath P, Shammas NW, Brilakis ES, Banerjee S. Comparison of Lower Extremity Endovascular Intervention Outcomes in Women Versus Men. *Am J Cardiol.* 2017;119(3):490-6.

204. Klaphake S, de Leur K, Mulder PGH, Ho GH, de Groot HGW, Veen EJ, et al. Life Expectancy and Outcome of Different Treatment Strategies for Critical Limb Ischemia in the Elderly Patients. *Ann Vasc Surg.* 2018;46:241-8.

205. Lejay A, Schaeffer M, Georg Y, Lucereau B, Roussin M, Girsowicz E, et al. Gender related Long-term Differences after Open Infrainguinal Surgery for Critical Limb Ischemia. *Eur J Vasc Endovasc Surg.* 2015;50(4):506-12.

206. Ohmine T, Iwasa K, Yamaoka T. Strategy of Revascularization for Critical Limb Ischemia Due to Infragenicular Lesions-Which Should Be Selected Firstly, Bypass Surgery or Endovascular Therapy? *Ann Vasc Dis.* 2015;8(4):275-81.

207. Senda K, Miura T, Minamisawa M, Ueki Y, Mochidome T, Nomi H, et al. Predictive Value of Underweight Status for Patients With Peripheral Artery Disease With Claudication. *Angiology.* 2017:3319717736627.

208. Shiraki T, Iida O, Takahara M, Okamoto S, Kitano I, Tsuji Y, et al. Predictive scoring model of mortality after surgical or endovascular revascularization in patients with critical limb ischemia. *J Vasc Surg.* 2014;60(2):383-9.

209. Sprengers RW, Janssen KJ, Moll FL, Verhaar MC, van der Graaf Y. Prediction rule for cardiovascular events and mortality in peripheral arterial disease patients: data from the prospective Second Manifestations of ARTerial disease (SMART) cohort study. *J Vasc Surg.* 2009;50(6):1369-76.

210. Takeji Y, Yamaji K, Tomoi Y, Okazaki J, Tanaka K, Nagae A, et al. Impact of Frailty on Clinical Outcomes in Patients With Critical Limb Ischemia. *Circ Cardiovasc Interv.* 2018.

211. Geller SE, Koch A, Pellettieri B, Carnes M. Inclusion, analysis, and reporting of sex and race/ethnicity in clinical trials: have we made progress? *J Womens Health.* 2011;20(3):315-20.

212. Lundberg G, Mehta L, Sanghani R, Patel H, Aggarwal N, Aggarwal N, et al. Heart Centers for Women: Historical Perspective on Formation and Future Strategies to Reduce Cardiovascular Disease. *Circulation.* 2018;138(11):1155-65.

213. Freisinger E, Malyar NM, Reinecke H, Lawall H. Impact of diabetes on outcome in critical limb ischemia with tissue loss: a large-scaled routine data analysis. *Cardiovasc Diabetol.* 2017;16(1):41.

214. Luders F, Bunzemeier H, Engelbertz C, Malyar NM, Meyborg M, Roeder N, et al. CKD and Acute and Long-Term Outcome of Patients with Peripheral Artery Disease and Critical Limb Ischemia. *Clin J Am Soc Nephrol.* 2016;11(2):216-22.

215. Richter L, Freisinger E, Lüders F, Gebauer K, Meyborg M, Malyar NM. Impact of diabetes type on treatment and outcome of patients with peripheral artery disease:. *J Diabetes Vasc Dis.* 2018.

216. Wasmer K, Unrath M, Kobe J, Malyar NM, Freisinger E, Meyborg M, et al. Atrial fibrillation is a risk marker for worse in-hospital and long-term outcome in patients with peripheral artery disease. *Int J Cardiol.* 2015;199:223-8.

217. Si S, Golledge J, Norman P, Nelson M, Chew D, Ademi Z, et al. Prevalence and Outcomes of Undiagnosed Peripheral Arterial Disease Among High Risk Patients in Australia: An Australian REACH Sub-Study. *Heart Lung Circ.* 2018.

218. Winkel TA, Hoeks SE, Schouten O, Zeymer U, Limbourg T, Baumgartner I, et al. Prognosis of atrial fibrillation in patients with symptomatic peripheral arterial disease: data from the REduction of Atherothrombosis for Continued Health (REACH) Registry. *Eur J Vasc Endovasc Surg.* 2010;40(1):9-16.

219. Suckow BD, Kraiss LW, Schanzer A, Stone DH, Kalish J, DeMartino RR, et al. Statin therapy after infrainguinal bypass surgery for critical limb ischemia is associated with improved 5-year survival. *J Vasc Surg.* 2015;61(1):126-33.

220. Goodney PP, Nolan BW, Schanzer A, Eldrup-Jorgensen J, Stanley AC, Stone DH, et al. Factors associated with death 1 year after lower extremity bypass in Northern New England. *J Vasc Surg.* 2010;51(1):71-8.

221. Vyas MV, Mrkobrada M, Donner A, Hackam DG. Underrepresentation of peripheral artery disease in modern cardiovascular trials: systematic review and meta-analysis. *Int J Cardiol.* 2013;168(5):4875-6.

222. Feinglass J, McDermott MM, Foroohar M, Pearce WH. Gender differences in interventional management of peripheral vascular disease: evidence from a blood flow laboratory population. *Ann Vasc Surg.* 1994;8(4):343-9.

223. Parvar SL, Nicholls SJ, Lincoff AM, Menon V, Riesmeyer JS, Ruotolo G, et al. Abstract 19202: Risk Factor Control and Major Adverse Cardiovascular Events in Patients With Peripheral Arterial Disease. *Circulation.* 2017;136.

224. Agarwal S, Pitcavage JM, Sud K, Thakkar B. Burden of Readmissions Among Patients With Critical Limb Ischemia. *J Am Coll Cardiol.* 2017;69(15):1897-908.

225. Malyar N, Furstenberg T, Wellmann J, Meyborg M, Luders F, Gebauer K, et al. Recent trends in morbidity and in-hospital outcomes of in-patients with peripheral arterial disease: a nationwide population-based analysis. *Eur Heart J.* 2013;34(34):2706-14.

226. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med.* 2018;379(22):2097-107.

227. Steg PG, Szarek M, Bhatt DL, Bittner VA, Bregeault MF, Dalby AJ, et al. Effect of Alirocumab on Mortality After Acute Coronary Syndromes. *Circulation.* 2019;140(2):103-12.

228. Roeters van Lennep JE, Westerveld HT, Erkelens DW, van der Wall EE. Risk factors for coronary heart disease: implications of gender. *Cardiovasc Res.* 2002;53(3):538-49.

229. Appelman Y, van Rijn BB, Ten Haaf ME, Boersma E, Peters SA. Sex differences in cardiovascular risk factors and disease prevention. *Atherosclerosis.* 2015;241(1):211-8.

230. Ramkumar N, Suckow BD, Brown JR, Sedrakyan A, MacKenzie T, Stone DH, et al. Role of Sex in Determining Treatment Type for Patients Undergoing Endovascular Lower Extremity Revascularization. *J Am Heart Assoc.* 2019;8(17):e013088.

231. Hiatt WR, Hess CN, Bonaca MP. Heterogeneity of Risk and Benefit in Subgroups of COMPASS: Relatively Similar But Absolutely Different. *J Am Coll Cardiol.* 2019;73(25):3292-4.

232. Vartanian SM, Conte MS. Surgical intervention for peripheral arterial disease. *Circ Res.* 2015;116(9):1614-28.

233. Thukkani A, Kinlay, S. Endovascular Intervention for Peripheral Artery Disease. *Circ Res.* 2015;116(9):1599-613.

234. Tang L, Paravastu SCV, Thomas SD, Tan E, Farmer E, Varcoe RL. Cost Analysis of Initial Treatment With Endovascular Revascularization, Open Surgery, or Primary Major Amputation in Patients With Peripheral Artery Disease. *J Endovasc Ther.* 2018;25(4):504-11.

235. Adam DJ, Beard JD, Cleveland T, Bell J, Bradbury AW, Forbes JF, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. *Lancet.* 2005;366(9501):1925-34.

236. Jones W, Dolor, RJ, Hasselblad, V, Vemulapalli, S, Subherwal, S, Schmit, K, Heidenfelder, B, Patel, MR. Comparative Effectiveness of Endovascular and Surgical Revascularization for Patients With Peripheral Artery Disease and Critical Limb Ischemia: Systematic Review of Revascularization in Critical Limb Ischemia. *Am Heart J.* 2014;167(4):489-98.

237. Henderson T, Shepheard J, Sundararajan V. Quality of diagnosis and procedure coding in ICD-10 administrative data. *Med Care.* 2006;44(11):1011-9.

238. Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: A survival prediction model to facilitate clinical decision making. *J Vasc Surg.* 2010;51(5 Suppl):52s-68s.

239. Londero L, Høgh A, Houlind K, Lindholt J. Danish Trends in Major Amputation After Vascular Reconstruction in Patients With Peripheral Arterial Disease 2002-2014. *Eur J Vasc Endovasc Surg.* 2019;57(1):111-20.

240. Jones W, Mi X, Qualls L, Vemulapalli S, Peterson E, Patel M, et al. Trends in Settings for Peripheral Vascular Intervention and the Effect of Changes in the Outpatient Prospective Payment System. *J Am Coll Cardiol.* 2015;65(9):920-7.

241. Sundaram V, Bloom C, Zakeri R, Halcox J, Cohen A, Bowrin K, et al. Temporal trends in the incidence, treatment patterns, and outcomes of coronary artery disease and peripheral artery disease in the UK, 2006–2015. *Eur Heart J.* 2020;41(17):1636-49.

242. Soden PA, Zettervall SL, Shean KE, Vouyouka AG, Goodney PP, Mills JL, et al. Regional Variation in Outcomes for Lower Extremity Vascular Disease in the Vascular Quality Initiative (VQI). *J Vasc Surg.* 2017;66(3):810-8.

243. Venermo M, Sprynger M, Desormais I, Bjorck M, Brodmann M, Cohnert T, et al. Follow-up of patients after revascularisation for peripheral arterial diseases: a consensus document from the European Society of Cardiology Working Group on Aorta and Peripheral Vascular Diseases and the European Society for Vascular Surgery. *Eur J Prev Cardiol.* 2019;26(18):1971-84.

244. Sobieszczyk P, Eisenhauer A. Management of patients after endovascular interventions for peripheral artery disease. *Circulation.* 2013;128(7):749-57.

245. Tsai TT, Rehring TF, Rogers RK, Shetterly SM, Wagner NM, Gupta R, et al. The Contemporary Safety and Effectiveness of Lower Extremity Bypass Surgery and Peripheral Endovascular Interventions in the Treatment of Symptomatic Peripheral Arterial Disease. *Circulation.* 2015;132(21):1999-2011.

246. Bonaca MP, Creager MA. Antithrombotic Therapy and Major Adverse Limb Events in Peripheral Artery Disease: A Step Forward. *J Am Coll Cardiol.* 2018;71(20):2316-8.

247. ClinicalTrials.gov [Internet]. National Library of Medicine (US)- Identifier NCT02504216. Efficacy and Safety of Rivaroxaban in Reducing the Risk of Major Thrombotic Vascular Events in Subjects With Symptomatic Peripheral Artery Disease Undergoing

Peripheral Revascularization Procedures of the Lower Extremities (VOYAGER PAD) 2018 [16/11/2019]. Available from: https://clinicaltrials.gov/ct2/show/NCT02504216.

248. Sanon S, Lenihan DJ, Mouhayar E. Peripheral arterial ischemic events in cancer patients. *Vasc Med.* 2011;16(2):119-30.

249. Chen Q, Smith CY, Bailey KR, Wennberg PW, Kullo IJ. Disease Location Is Associated With Survival in Patients With Peripheral Arterial Disease. *J Am Heart Assoc.* 2013;2(5).

250. Chen Q, Shi Y, Wang Y, Li X. Patterns of Disease Distribution of Lower Extremity Peripheral Arterial Disease. *Angiology.* 2014.

251. Popplewell M, Davies H, Jarrett H, Bate G, Grant M, Patel S, et al. Bypass Versus Angio Plasty in Severe Ischaemia of the Leg - 2 (BASIL-2) Trial: Study Protocol for a Randomised Controlled Trial. *Trials.* 2016;17(11).

252. Australian Institute of Health and Welfare 2011. Cardiovascular disease: Australian facts 2011. *Cardiovascular disease series Cat no CVD 53 Canberra: AIHW.*

253. Zhao Y, Dempsey K. Causes of inequality in life expectancy between Indigenous and non-Indigenous people in the Northern Territory, 1981–2000: a decomposition analysis. *Medical Journal of Australia.* 2019;184(10):490-4.

254. Australian Institute of Health and Welfare. Cardiovascular disease, diabetes and chronic kidney disease—Australian facts: Aboriginal and Torres Strait Islander people. Cardiovascular, diabetes and chronic kidney disease series. *AIHW.* 2015.

255. Shemesh T, Rowley KG, Piers LS, Best JD, O'Dea K. Low high-density lipoprotein-cholesterol is the most prevalent metabolic abnormality for Australian Aboriginal men and women even when lean. *Eur J Cardiovasc Prev Rehabil.* 2008;15(1):49-51.

256. Barter P, Gotto AM, LaRosa JC, Maroni J, Szarek M, Grundy SM, et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *N Engl J Med.* 2007;357(13):1301-10.

257. Bhatt A, Rohatgi A. HDL Cholesterol Efflux Capacity: Cardiovascular Risk Factor and Potential Therapeutic Target. *Curr Atheroscler Rep.* 2016;18(1):2.

258. He Y, Kothari V, Bornfeldt KE. High-Density Lipoprotein Function in Cardiovascular Disease and Diabetes Mellitus. 2018.

259. Rohatgi A, Khera A, Berry JD, Givens EG, Ayers CR, Wedin KE, et al. HDL Cholesterol Efflux Capacity and Incident Cardiovascular Events. *N Engl J Med.* 2014;375(25):2383-93.

260. Takata K, Duong M, Shemesh T, Kim SW, Lyons JG, Sidharta SL, et al. Abstract 15485: Impaired Cholesterol Efflux Capacity in Aboriginal Australians - Implications for Elevated Cardiovascular Risk in Indigenous Populations. *Circulation.* 2018;138:A15485.

261. McGrady M, Krum H, Carrington MJ, Stewart S, Zeitz C, Lee GA, et al. Heart failure, ventricular dysfunction and risk factor prevalence in Australian Aboriginal peoples: the Heart of the Heart Study. *Heart.* 2012;98(21):1562-7.

262. Brown A, Carrington MJ, McGrady M, Lee G, Zeitz C, Krum H, et al. Cardiometabolic risk and disease in Indigenous Australians: the heart of the heart study. *Int J Cardiol.* 2014;171(3):377-83.

263. Rose GA. ISCHEMIC HEART DISEASE. CHEST PAIN QUESTIONNAIRE. *Milbank Mem Fund Q.* 1965;43:32-9.

264. National Health and Medical Research Council. Australian guidelines to reduce health risks from drinking alcohol | NHMRC. *Canberra: Commonwealth of Australia.* 2009.

265. Luke JN, Brown A, Daniel M, O'Dea K, Best JD, Jenkins AJ, et al. The metabolic syndrome and CVD outcomes for a central Australian cohort. *Diabetes Res Clin Pract.* 2013;100(3):e70-3.

266. Kidney Health Australia. Chronic Kidney Disease (CKD) Management in General Practice. 3rd Edition 2015 [12/11/2019]. Available from: https://kidney.org.au/cms_uploads/docs/ckdm-in-gp-handbook.pdf.

267. Khera AV, Cuchel M, de la Llera-Moya M, Rodrigues A, Burke MF, Jafri K, et al. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. *N Engl J Med.* 2011;364(2):127-35.

268. Sankaranarayanan S, Kellner-Weibel G, de la Llera-Moya M, Phillips MC, Asztalos BF, Bittman R, et al. A sensitive assay for ABCA1-mediated cholesterol efflux using BODIPY-cholesterol. *J Lipid Res.* 2011;52(12):2332-40.

269. Li XM, Tang WH, Mosior MK, Huang Y, Wu Y, Matter W, et al. Paradoxical association of enhanced cholesterol efflux with increased incident cardiovascular risks. *Arterioscler Thromb Vasc Biol.* 2013;33(7):1696-705.

270. Koba S, Ayaori M, Uto-Kondo H, Furuyama F, Yokota Y, Tsunoda F, et al. Beneficial Effects of Exercise-Based Cardiac Rehabilitation on High-Density Lipoprotein-Mediated Cholesterol Efflux Capacity in Patients with Acute Coronary Syndrome. *J Atheroscler Thromb.* 2016;23(7):865-77.

271. Boyer M, Lévesque V, Poirier P, Marette A, Mitchell PL, Mora S, et al. Longitudinal Changes in Cholesterol Efflux Capacities in Patients With Coronary Artery Disease Undergoing Lifestyle Modification Therapy. *J Am Heart Assoc.* 2018;7(11).

272. von Eckardstein A. A Novel Biomarker Approach to Exploit HDL for Risk Assessment. *J Am Coll Cardiol.* 2019;73(17).

273. Shaw JA, Bobik A, Murphy A, Kanellakis P, Blombery P, Mukhamedova N, et al. Infusion of reconstituted high-density lipoprotein leads to acute changes in human atherosclerotic plaque. *Circ Res.* 2008;103(10):1084-91.

274. Sarzynski MA, Ruiz-Ramie JJ, Barber JL, Slentz CA, Apolzan JW, McGarrah RW, et al. Effects of Increasing Exercise Intensity and Dose on Multiple Measures of HDL (High-Density Lipoprotein) Function. *Arterioscler Thromb Vasc Biol.* 2018;38(4):943-52.

275. Albaghdadi MS, Wang Z, Gao Y, Mutharasan RK, Wilkins J. High-Density Lipoprotein Subfractions and Cholesterol Efflux Capacity Are Not Affected by Supervised Exercise but Are Associated with Baseline Interleukin-6 in Patients with Peripheral Artery Disease. *Front Cardiovasc Med.* 2017;4:9.

276. Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, et al. Measurement and Interpretation of the Ankle-Brachial Index. *Circulation.* 2012;126(24):2890-909.

277. Calabria B, Korda RJ, Lovett RW, Fernando P, Martin T, Malamoo L, et al. Absolute cardiovascular disease risk and lipid-lowering therapy among Aboriginal and Torres Strait Islander Australians. *Medical Journal of Australia.* 2018;209(1):35-41.

278. Hua X, McDermott R, Lung T, Wenitong M, Tran-Duy A, Li M, et al. Validation and recalibration of the Framingham cardiovascular disease risk models in an Australian Indigenous cohort. *Eur J Prev Cardiol.* 2017;24(15):1660-9.

279. Maple-Brown L, Cunningham J, Dunne K, Whitbread C, Howard D, Weeramanthri T, et al. Complications of diabetes in urban Indigenous Australians: the DRUID study. *Diabetes Res Clin Pract.* 2008;80(3):455-62.

280. Singh TP, Moxon JV, Healy GN, Cadet-James Y, Golledge J. Presentation and outcomes of indigenous Australians with peripheral artery disease. *BMC Cardiovasc Disord.* 2018;18(1):94.

281. Australian Bureau of Statistics AIHW. The Health and Welfare of Australia's Aboriginal and Torres Strait Islander Peoples. Canberra: ABS and AIHW. 2008.

282. Fowkes FG, Price JF, Stewart MC, Butcher I, Leng GC, Pell AC, et al. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. *Jama.* 2010;303(9):841-8.

283. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, ClevelandJr JC, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. *Circulation.* 2019;74(1):104-32.

284. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of Clinical Classification Schemes for Predicting Stroke: Results From the National Registry of Atrial Fibrillation. *Jama.* 2019;285(22):2864-70.

285. Piccini JP, Stevens SR, Chang Y, Singer DE, Lokhnygina Y, Go AS, et al. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R(2)CHADS(2) index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study cohorts. *Circulation.* 2013;127(2):224-32.

286. Tabata N, Yamamoto E, Hokimoto S, Yamashita T, Sueta D, Takashio S, et al. Prognostic Value of the CHADS2 Score for Adverse Cardiovascular Events in Coronary Artery Disease Patients Without Atrial Fibrillation-A Multi-Center Observational Cohort Study. *J Am Heart Assoc.* 2017;6(8).

287. Li Y, Wang J, Lv L, Xu C, Liu H. Usefulness of the CHADS2 and R2CHADS2 scores for prognostic stratification in patients with coronary artery disease. *Clin Interv Aging.* 2018;13:565-71.

288. Poci D, Hartford M, Karlsson T, Herlitz J, Edvardsson N, Caidahl K. Role of the CHADS2 score in acute coronary syndromes: risk of subsequent death or stroke in patients with and without atrial fibrillation. *Chest.* 2012;141(6):1431-40.

289. van der Leeuw J, Ridker PM, van der Graaf Y, Visseren FL. Personalized cardiovascular disease prevention by applying individualized prediction of treatment effects. *Eur Heart J.* 2014;35(13):837-43.

290. Conway DS, Lip GY. Comparison of outcomes of patients with symptomatic peripheral artery disease with and without atrial fibrillation (the West Birmingham Atrial Fibrillation Project). *Am J Cardiol.* 2004;93(11):1422-5, a10.

291. Poldervaart JM, Langedijk M, Backus BE, Dekker IMC, Six AJ, Doevendans PA, et al. Comparison of the GRACE, HEART and TIMI score to predict major adverse cardiac events in chest pain patients at the emergency department. *Int J Cardiol.* 2017;227:656-61.
292. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604-12.
293. Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med.* 2008;27(2):157-72.
294. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2019.
295. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med.* 2015;374(11):1094.
296. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med.* 2016;375(19):1834-44.
297. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med.* 2016;375(4):311-22.
298. Mega JL, Braunwald E, Wiviott SD, Bassand J-P, Bhatt DL, Bode C, et al. Rivaroxaban in Patients with a Recent Acute Coronary Syndrome. *N Engl J Med.* 2012;366:9-19.
299. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke.* 2018;49(3):e46-e110.
300. Coppens M, Eikelboom JW, Hart RG, Yusuf S, Lip GY, Dorian P, et al. The CHA2DS2-VASc score identifies those patients with atrial fibrillation and a CHADS2 score of 1 who are unlikely to benefit from oral anticoagulant therapy. *Eur Heart J.* 2013;34(3):170-6.

301. Kurtul A, Acikgoz SK. Validation of the CHA2DS2-VASc Score in Predicting Coronary Atherosclerotic Burden and In-Hospital Mortality in Patients With Acute Coronary Syndrome. *Am J Cardiol.* 2017;120(1):8-14.

302. Kim KH, Kim W, Hwang SH, Kang WY, Cho SC, Jeong MH. The CHA2DS2VASc score can be used to stratify the prognosis of acute myocardial infarction patients irrespective of presence of atrial fibrillation. *J Cardiol.* 2015;65(2):121-7.

303. Reboussin DM, Allen NB, Griswold ME, Guallar E, Hong Y, Lackland DT, et al. Systematic Review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension.* 2018;71(6):e116-e35.

304. Chao TF, Chen SA. Using the scoring schemes in the right way: the dynamic assessment of stroke and bleeding risk in patients with atrial fibrillation. J Thorac Dis. 102018. p. S2089-91.

305. Chao TF, Lip GYH, Liu CJ, Lin YJ, Chang SL, Lo LW, et al. Relationship of Aging and Incident Comorbidities to Stroke Risk in Patients With Atrial Fibrillation. *J Am Coll Cardiol.* 2018;71(2):122-32.

306. Lip GYH, Skjoth F, Nielsen PB, Kjaeldgaard JN, Larsen TB. The HAS-BLED, ATRIA, and ORBIT Bleeding Scores in Atrial Fibrillation Patients Using Non-Vitamin K Antagonist Oral Anticoagulants. *Am J Med.* 2018;131(5):574.e13-.e27.

307. Lip GYH, Lane DA. Matching the NOAC to the Patient: Remember the Modifiable Bleeding Risk Factors. *J Am Coll Cardiol.* 2015;66(21):2282-4.

308. Gardner AW, Skinner JS, Cantwell BW, Smith LK. Progressive vs single-stage treadmill tests for evaluation of claudication. *Med Sci Sports Exerc.* 1991;23(4):402-8.

309. Spertus J, Jones P, Poler S, Rocha-Singh K. The peripheral artery questionnaire: a new disease-specific health status measure for patients with peripheral arterial disease. *Am Heart J.* 2004;147(2):301-8.