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ORIGINAL ARTICLE

Prevalence and Outcomes of Undiagnosed Peripheral Arterial Disease Among High Risk Patients in Australia: An Australian REACH Sub-Study

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Background Compared with other manifestations of cardiovascular disease, peripheral arterial disease (PAD) is underdiagnosed. This study aims to investigate the prevalence, risk profile and cardiovascular outcomes of undiagnosed PAD in Australian general practices.

Method A sub-study of the Australian Reduction of Atherothrombosis for Continued Health (REACH) Registry, a prospective cohort study of patients at high risk of atherothrombosis recruited from Australian general practices. Eligible patients for this study had no previous clinical diagnosis of PAD and had an ankle-brachial index (ABI) $\leq$1.4 at recruitment.

Results Peripheral arterial disease was undiagnosed in 34% Australian REACH participants, 28% patients had low ABI (ABI $<$ 0.9) and 11% had intermittent claudication (IC) based on responses to the Edinburgh Claudication Questionnaire (ECQ). We found no significant differences in risk factor control between patient with or without PAD. Intermittent claudication patients had higher risks of non-fatal cardiovascular events and PAD interventions at one year, whereas all-cause mortality rate was higher among patients with ABI$<$0.9, especially in those who also reported IC. Finally, an ABI $<$ 0.9, together with poorly controlled risk factors were independent predictors of incident IC at one year.

Conclusions This study suggests a high rate of undiagnosed PAD among high risk patients in Australian primary health care. These patients are at high risk of events and therefore would potentially benefit from better secondary prevention measures.

Keywords Peripheral arterial disease • Australian primary health care • Ankle-brachial index • Intermittent claudication

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Introduction

Peripheral arterial disease (PAD) is an indicator of systemic atherosclerosis and has a major impact on patients' quality of life by limiting mobility [1]. It is the third leading atherosclerotic cardiovascular morbidity following coronary heart disease and stroke [2]. It exists at a pandemic scale. A systematic review reported an estimated global prevalence of 202 million individuals in the year 2010 [3]. The prevalence of PAD increases with age, especially after the fifth decade of life [4]. PAD is two to five times more prevalent in patients with existing cardiovascular disease than those without [4]. In Australia, the age-standardised prevalence of PAD in older men has been estimated as 16% [5].

The ankle-brachial index (ABI) is used widely as a screening and diagnostic test for PAD in both epidemiological studies and in clinical practice [6]. An ABI below 0.9 is generally considered diagnostic of PAD, while an ABI above 1.4 is commonly used as a cut-off for defining non-compressible ankle arteries [7]. Usually, clinicians rely on symptoms, such intermittent claudication (IC), and clinical signs to diagnose PAD. The Edinburgh Claudication Questionnaire (ECQ) is a validated screening and diagnostic tool for IC [8]. It is worth noting that many patients with PAD are asymptomatic [9]. Also, leg pain can be caused by a number of conditions other than PAD [10]. Screening for PAD in routine clinical practice in Australia is not currently recommended by Royal Australian College of General Practice (RACGP) [11].

Compared with other manifestations of cardiovascular disease, PAD is under-diagnosed due to the lack of awareness of the disease among patients and the limited health services allocated to the diagnosis of PAD (e.g. screening) [12]. Importantly, PAD patients are usually subject to relatively poor control of cardiovascular risk factors (blood pressure, serum lipid, glucose and smoking cessation) [13,14], which contributes to their increasing risk of cardiovascular events. A low ABI (< 0.9) has been consistently associated with increased risks of cardiovascular morbidity and mortality [4]. Relatively few studies have investigated the association of IC, as defined by the ECQ, with outcome. Some studies have reported a higher risk of fatal and non-fatal cardiovascular events among IC patients [15,16]. One US study, surprisingly, reported worse functional performance (6-minute walk test) and poorer quality of life (SF-36) among people with PAD who never experienced exertional leg symptoms compared to those with IC [16].

There has been no previous study of the prevalence and cardiovascular profiles of people with undiagnosed PAD in Australian primary health care. In the current study, we investigated: 1) the prevalence of an ABI <0.9 (diagnostic of PAD) and IC (using ECQ) among patients with a history or at high risk of cardiovascular disease (CVD) in Australian general practices; 2) the control of risk factors among patients with and without PAD; 3) the health outcomes (including all-cause mortality, non-fatal MI or stroke and PAD interventions) among patients with and without PAD and symptom of IC; and 4) the predictors of new onset of IC at one year.

Method

The Reduction of Atherothrombosis for Continued Health (REACH) registry is an international outpatient study of patients either with CVD (i.e. coronary artery disease (CAD), cerebral vascular disease (CerVD) and PAD) or at high risk of developing cardiovascular disease with at least three identifiable risk factors [17]. Australia, as one of the major REACH collaborators, recruited over two thousand patients and was the only country that recruited patients from primary health care (general practices). Australia was the only country that performed a comprehensive assessment of PAD (ABI measurements and ECQ) on all participants. This information is therefore unique and crucial to inform policy concerning screening for PAD in primary health care.

For the present analysis, a subgroup of patients from the REACH registry was selected if they 1) did not have clinical diagnosis of PAD at recruitment and; 2) had an ABI ≤1.4 at baseline; and 3) responded to the ECQ at baseline. The study method has been reported elsewhere [18,19]. Briefly, baseline seated blood pressure, and fasting glucose and cholesterol levels were measured. All participants were re-evaluated at 12 months to ascertain their health outcomes via telephone follow-up using a standardised case report form. All-cause mortality included death of any cause at one year. Non-fatal events included non-fatal myocardial infarction, non-fatal stroke, and hospitalisation for cardiac procedures. Peripheral arterial disease events recorded included lower limb amputation; peripheral bypass grafting; or other interventions for PAD or a new clinical diagnosis of PAD or worsening of IC that resulted in hospitalisation.

The lower ABI readings of the two limbs was used in the following analysis. Ankle-brachial index of <0.9 was used as the cut-off for the diagnosis of PAD. Based on patients' response to the ECQ [8], IC positive was assigned to patients if they reported: discomfort in the legs on walking (YES to Question 1); no pain on standing or sitting (NO to Question 2); pain in legs when walking uphill or hurrying (YES to Question 3); leg pain that disappears in 10 minutes if standing still and (YES to Question 5); the pain was located in the calf region/thigh or buttock.

Based on the results of ABI and ECQ screening at baseline, patients were categorised into four groups: ABI− & IC-; ABI- & IC+; ABI+ & IC-; and ABI+ & IC+. The agreement between ABI measurement and ECQ response was examined using Cohen's kappa statistics. Control of risk factors at recruitment was assessed using treatment to target criteria: systolic and diastolic blood pressure <140 mmHg and <90 mmHg respectively, glucose level <6.1 mmol/L, total cholesterol level <5.2 mmol/L, and smoking cessation was defined as 'stopping smoking for more than 12 months'.

Descriptive analysis was applied to summarise patients' age, sex, CVD diagnosis at recruitment, the number and proportion of patients with risk factors under control as well as all-cause mortality and cardiovascular events at one year. Chi-square test and Fisher's exact test were used where

appropriate. Cox proportional regressions were applied to investigate the associations between ABI and IC with outcomes. All regression models were adjusted for CVD diagnosis, sex, age and the control of risk factors. The proportional of hazards (PH) assumption was tested using the Schoenfeld residuals test. Where the test indicated violation of the PH assumption, we stratify the regression model on the non-proportional predictor. Finally, in a subset of patients with a negative ECQ at baseline, logistic regression models were applied to investigate the determinants of new IC onset at 1 year, adjusting for CVD diagnosis at recruitment, sex, age and control of risk factors.

Results

Altogether, there are 2,489 REACH participants eligible for this study. Among 2,489 eligible participants at baseline, mean ABI was 0.95 (SD: 0.21). About 28% of them were ABI+ (ABI < 0.9), and 11% (271/2,489) were IC+. The prevalence of IC was 8.6% (154/1,796) among ABI- patients and 17% (117/693) among ABI+ patients (Table 1). Female participants were more likely to be ABI+ compared to male patients (31% vs 26%). A higher proportion of IC- patients than IC+ patients had CerVD (15% vs 9%), whereas IC+ patients were more likely to have CAD compared to IC- patients (68% vs 64%) (Table 1).

The agreement between the ABI and IC measurement was poor with Cohan's kappa coefficient of 0.10 (SE: 0.02).

The adequacy of risk factors control at baseline is summarised in Table 2. Overall, no significant differences were observed among patients with different ABI and IC status. An overall indicator of risk factors control (no less than three out of the above five risk factors managed to target) yielded no significant difference either.

Table 3 summarises all-cause mortality, non-fatal cardiovascular and PAD events at one year follow-up by ABI and IC status. Overall, the all-cause mortality and PAD event rates were low at 2% and 1.2% respectively, whereas the non-fatal event rate remained relatively high at around 9%. ABI+ patients had higher all-cause mortality (2.9% vs 1.6%) and PAD event rates (2.1% VS 0.9%) than ABI- patients. IC+ patients were at higher risk of non-fatal events (11.8% vs 8.3%) and PAD events than IC- patients (4.8% vs 0.8%). Of all patient subgroups, the ABI+ IC+ patients were at highest risks of all-cause mortality (6%) and PAD events (7%).

Based on the results of the Schoenfeld residuals tests, we stratified the all-cause mortality cox regression model by CVD diagnosis at recruitment and the non-fatal events model by risk factors control. No violation of the PH assumption was found in the PAD events model. The final Cox regression models demonstrated complex associations between outcomes and patient groups (Table 4). Among IC+ ABI- and IC+ ABI+ patients, the risks of PAD events were seven and nine times higher than those IC- ABI- patients respectively. The risks of all-cause mortality among the IC+ ABI+ was four times as high as those IC- ABI- patients.

Table 1 Characteristics of Australian REACH participants by ABI & IC status.

Patient groups	Total N	Age [mean (SD)]	Sex N (row%/col%)			CVD diagnosis at recruitment N (row%/col%)				
			Males	Females	P[$]	Non-CAD&CerVD	CAD	CerVD	CAD & CerVD	P[$]
Total	2,489	72.8 (8.8)	1,624 (65.3%/100%)	864 (34.7%/100%)		286 (11.5%/100%)	1,605 (64.5%/100%)	350 (14.1%/100%)	248 (10.0%/100%)	
ABI- IC-	1,642	73.0 (8.7)	1,095 (66.7%/67.4%)	546 (33.3%/63.2%)	0.007	184 (11.2%/64.3%)	1,051 (64.0%/65.5%)	251 (15.3%/71.7%)	156 (9.5%/62.9%)	0.04
ABI- IC+	154	72.0 (9.1)	111 (72.1%/6.8%)	43 (27.9%/5.0%)		23 (14.9%/8.0%)	98 (63.6%/6.1%)	14 (9.1%/4.0%)	19 (12.3%/7.7%)	
ABI+ IC-	576	72.9 (8.8)	348 (60.4%/21.4%)	228 (39.6%/26.4%)		63 (10.9%/22.0%)	370 (64.2%/23.1%)	76 (13.2%/21.7%)	67 (11.6%/27.0%)	
ABI+ IC+	117	71.9 (10.3)	70 (59.8%/4.3%)	47 (40.2%/5.4%)		16 (13.7%/5.6%)	86 (73.5%/5.4%)	9 (7.7%/2.6%)	6 (5.1%/2.4%)	
ABI-	1,796	72.8 (9.1)	1,206 (67.2%/74.3%)	589 (32.8%/68.2%)	0.001	207 (11.5%/72.4%)	1,149 (64.0%/71.6%)	265 (14.8%/75.7%)	175 (9.7%/70.6%)	0.426
ABI+	693	72.9 (8.7)	418 (60.3%/25.7%)	275 (39.7%/31.2%)		79 (11.4%/27.6%)	456 (65.8%/28.4%)	85 (12.3%/24.3%)	73 (10.5%/29.4%)	
IC-	2,218	73.0 (8.7)	1,443 (65.1%/88.9%)	774 (34.9%/89.6%)	0.579	247 (11.1%/86.4%)	1,421 (64.1%/88.5%)	327 (14.7%/93.4%)	223 (10.1%/89.9%)	0.022
IC+	271	72.0 (9.6)	181 (66.8%/11.1%)	90 (33.2%/10.4%)		39 (14.4%/13.6%)	184 (67.9%/11.5%)	23 (8.5%/6.6%)	25 (9.2%/10.1%)	

Abbreviations: REACH, Reduction of Atherothrombosis for Continued Health; CAD, coronary artery disease; CerVD, cerebral vascular disease; ABI, ankle brachial index; CVD, cardiovascular disease; IC, intermittent claudication.

[$]Chi-square test.

Table 2 ABI & IC status and risk factors control at baseline.

Patient groups	N	SBP control	DBP control	Glucose control	Cholesterol control	Non-smoker	RFs control*
ABI- IC-	1,642	788/1639 (48.1%)	1,328/1639 (81.0%)	452/653 (69.2%)	648/849 (76.3%)	1,493/1632 (91.5%)	1,019/1641 (62.1%)
ABI- IC+	154	78/154 (50.7%)	133/154 (86.4%)	45/64 (70.3%)	60/83 (72.3%)	139/152 (91.5%)	103/154 (66.9%)
ABI+ IC-	576	249/574 (43.4%)	486/573 (84.8%)	151/230 (65.7%)	223/298 (74.8%)	521/574 (90.8%)	347/576 (60.2%)
ABI+ IC+	117	48/117 (41.0%)	100/117 (85.4%)	32/50 (64.0%)	49/67 (73.1%)	100/116 (86.2%)	73/117 (62.4%)
P value#		0.1	0.08	0.67	0.79	0.28	0.51

Abbreviations: SBP, systolic blood pressure; DPB, diastolic blood pressure; RFs, risk factors; ABI, ankle brachial index; CVD, cardiovascular disease; IC, intermittent claudication

*More than 3/5 risk factors (SBP < 140 mmHg, DBP < 90 mmHg, Glucose < 6.1 mmol/L, cholesterol < 5.2 mmol/L and smoking cessation) controlled to target level at baseline.

#Chi-square test.

Table 3 ABI & IC status at baseline and health outcomes at one year.

Patient groups	n	All Cause Mortality		Non-fatal MI/Stroke or Hospitalisation*		PAD events^	
		N (%)	P	N (%)	P	N (%)	P
Total	**2,489**	**49 (2.0)**		**216 (8.7)**		**30 (1.2)**	
ABI- IC-	1,642	***29 (1.8%)***	***0.007***#	134 (8.2%)	0.244##	***11 (0.7%)***	***<0.001***#
ABI- IC+	154	***0***		17 (11.0%)		***5 (3.2%)***	
ABI+ IC-	576	***13 (2.3%)***		50 (8.7%)		***6 (1.0%)***	
ABI+ IC+	117	***7 (6.0%)***		15 (12.8%)		***8 (6.8%)***	
ABI+	696	***20 (2.9%)***	***0.05***##	65 (9.3%)	0.47##	***14 (2.1%)***	***0.02***##
ABI-	1,813	***30 (1.6%)***		153 (8.4%)		***16 (0.9%)***	
IC+	271	7 (2.6%)	0.441##	**32 (11.8%)**	***0.05***##	***13 (4.8%)***	***<0.001***##
IC-	2,218	42 (1.9%)		**184 (8.3%)**		***17 (0.8%)***	

Abbreviations: ABI, ankle brachial index; PAD, peripheral arterial disease; IC, intermittent claudication.

Statistically significant results ($p < 0.05$) are marked bold and italic.

*Non-fatal events include non-fatal MI, stroke and hospitalisations for cardiac procedures.

^PAD events include peripheral arterial procedures and related hospitalisations.

#Fisher's exact test.

##Chi-square test.

Symptomatic PAD at One-Year Follow-Up

Only IC- patients (n = 2,218) at baseline were included in the following analysis. At one-year, 2,031 eligible patients completed the ECQ. Of the 187 participants who did not respond to the ECQ, 41 died within one year (93.3% response rates). Comparisons of the 146 alive patients who did not respond to the ECQ and those who responded did not show any differences regarding age, gender (65% vs 62% being males), CVD diagnosis and ABI levels (26% vs 25% ABI +) at recruitment.

Of all the 2,031 responding patients, 6% (123/2,031) developed IC at one year. Among ABI+ patients, the odds of developing IC was 1.6 times as high as those with normal ABI (Table 4). Similarly, patients with poor control of CVD risk factors were more likely to develop IC at one year.

Discussion

More than a third (34%) of Australian REACH participants had undiagnosed PAD on the basis of either low ABI (28%) or the symptoms of IC (11%). We did not find significant differences in risk factor control between patient subgroups. Compared to ABI- and IC- patients, those who were ABI+ IC+ were nine times more likely to have PAD events and three times more likely to die of any cause during one year follow-up. Low ABI (ABI < 0.9), together with poorly controlled risk factors were independent predictors of incident IC at one year.

Underdiagnoses of PAD in Australian Primary Health Care

Among Australian REACH participants with no known PAD diagnosis at baseline, 28% had PAD based on an ABI < 0.9.

Table 4 Regression models of health outcomes at one year by ABI &IC status at baseline.

	All Cause Mortality[$]		Non-fatal MI/Stroke or hospitalisation[*,$$]		PAD events		Self-reported IC[#]	
	HR	CI	HR	CI	HR	CI	OR	CI
PAD status								
ABI- IC-	1.00		1.00		*1.00*		1.00	
ABI- IC+	-		**1.80**	**1.07, 3.04**	***7.67***	**2.47, 23.85**	**N/A**	
ABI+ IC-	1.45	0.72, 2.91	1.08	0.75, 1.56	*2.14*	0.74, 6.20	1.58	1.03, 2.43
ABI+ IC+	**3.61**	**1.45, 8.98**	1.48	0.79, 2.77	***9.98***	**3.43, 29.05**	**N/A**	
CVD diagnosis								
High risk[**]			1.00		1.00		1.00	
CerVD			1.61	0.72, 3.61	*3.32*	0.34, 32.34	0.54	0.24, 1.21
CAD			**2.79**	**1.40, 5.54**	*4.21*	0.56, 31.80	0.77	0.42, 1.40
CerVD + CAD			1.87	0.83, 4.22	*2.54*	0.23, 28.14	1.01	0.46, 2.20
Age	1.00	0.99, 1.00	1.01	1.00, 1.03	*1.01*	0.97, 1.06	1.00	0.97, 1.02
Sex	0.98	0.52, 1.87	0.96	0.70, 1.33	*0.93*	0.39, 2.20	1.38	0.91, 2.10
Poor RF control[^]	1.44	0.78, 2.66			***2.71***	**1.19, 6.15**	**1.55**	**1.03, 2.35**

Statistically significant results ($p < 0.05$) are marked bold and italic.

Abbreviations: HR, heart rate; ABI, ankle brachial index; CVD, cardiovascular disease; CerVD, cerebral vascular disease; CAD, coronary artery disease; MI, myocardial infarction; PAD, peripheral arterial disease; IC, intermittent claudication; RFs, risk factors; HR, harzard ratio; OR, odds ratio.

[*]Non-fatal events include non-fatal MI, stroke and hospitalisations for cardiac procedures.

[**]Patients with no existing CerVD or CAD.

[^]Less than 3/5 risk factors controlled to target levels.

[$]Model stratified CVD diagnosis.

[$$]Model stratified by poor RF control.

[#]Logistic regression applied.

This is similar to the findings of other studies. For example, a German study reported an overall PAD prevalence of 20% (ABI < 0.9) in general practice. In patients with a history of cardiovascular disease, the prevalence reached 29% [12]. Similarly, a UK study reported 28% of patients aged between 55 and 74 years were either IC or ABI screening positive from general practices [20].

We found that ABI+ patients were twice as likely to be IC+ than ABI- patients (17% vs 8%). However, our analysis further suggested poor agreement between ABI and IC screening results. Despite most studies reporting increased likelihood of exertional leg pain (including IC, atypical claudication and ischaemic leg pain) among patients with lower ABI, none of the subtypes of leg pain are specific for PAD diagnosis [21,22]. One study further concluded that PAD patients diagnosed by ABI screening in primary care are likely to be asymptomatic [22]. Therefore, more evidence is required to validate PAD symptom screening among high risk patients in primary health care.

Control of Cardiovascular Risk Factors Among High Risk Patients

Cardiovascular risk factor control is known to be poor in patients with PAD, compared to those with other manifestations of CVD [13,14]. The global REACH study reported worse risk profiles (SBP, DBP, glucose, total cholesterol and smoking cessation) in patients with PAD [18]. However, our analysis did not show any significant difference in risk factor control amongst a subgroup of patients by ABI and IC screenings. This may be because Australian REACH participants were recruited from general practices instead of from tertiary hospitals and specialist clinics as in other REACH participating countries. As primary health care providers, routine management of cardiovascular risk factors is strongly recommended and emphasised in Australian primary health care, especially for high risk patients [11]. For example, we observed a more than 90% non-smoking rate in Australian REACH participants compared to 85% reported in the global REACH study [18]. This could, to a large extent, be attributed to high level of advice provided from general practitioners to smokers within the Australian primary health care environment [23].

Nevertheless, our analysis indicated gaps in clinical management of blood pressure and blood glucose among high risk patients. The treatment target for SBP (< 140 mmHg) was not achieved in over half of study patients at baseline, despite more than 88% of them being prescribed at least one anti-hypertensive medication [19]. Similarly, more than a third of patients had serum glucose level higher than 6.1 mmol/L. Future studies should focus on potentially improving the management of cardiovascular risk factors in primary health care, especially among patients with PAD.

Comparison of Cardiovascular Events at One-Year Follow-Up

We observed a strong association between IC at baseline and PAD events, suggesting the majority of PAD-related procedures and hospitalisations being primarily symptom-driven. Our further analysis of incident IC, indicated that, besides overall control of cardiovascular risk factors, an ABI <0.9 is an independent predictor of IC at one year. This is consistent with previous findings that low ABI, worsening ABI, smoking and diabetes are major risk factors for IC [24]. Similar to previous studies [25,26], we found a high all-cause mortality rate among ABI+ patients (ABI < 0.9) and even higher rate among those also IC positive. Our study results also suggested higher non-fatal cardiovascular event rates among IC+ patients than IC- patients. It could be associated with the foundation in pathway of pain perception. It is reported that patients who are free of pain despite major arthrosclerosis at one site are more likely to be asymptomatic when other vascular sites are affected [4].

Limitations

This study had several limitations. First, the assessment of IC relied on patient's completion of the ECQ. Therefore, the study results were subject to the accuracy of the ECQ in diagnosing IC. However, the ECQ remains the recommended screening tool for IC in clinical practice. Second, the one-year health outcomes were derived from patients' self-report via interviews and telephone follow-ups. To mitigate recall bias, all self-reported cardiovascular events were verified through death and hospital admission records. Third, despite a relatively large sample size, the number of outcome events were low, especially the all-cause mortality and PAD events. Therefore, extended follow-up is required to enable further statistical analysis of the associations found. Finally, as discussed in previous publications [19,27], the participants recruited may not be representative of those presenting to all general practices in Australia.

Conclusion

In conclusion, this study suggests a high prevalence of undiagnosed PAD among high risk patients in Australian primary health care and that these patients have poor outcomes. Whether screening to identify these patients is warranted is yet to be adequately investigated.

Acknowledgement and Declaration

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