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Observational Study

Control of modifiable risk factors and major adverse cardiovascular events in people with peripheral artery disease and diabetes

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Abstract

BACKGROUND

People with diabetes and peripheral artery disease (PAD) have a high risk of major adverse cardiovascular events (MACE). Prior research suggests that medical therapies aimed to control modifiable risk factors are poorly implemented in patients with PAD.

AIM

To examine the association between the control of modifiable risk factors, estimated by the novel PAD-medical score, and the incidence of MACE in people with PAD and diabetes.

METHODS

Participants were recruited from out-patient clinics if they had a diagnosis of both PAD and diabetes. Control of reversible risk factors was assessed by a new composite measure, the PAD-medical score. This score takes into account the control of low-density lipoprotein cholesterol, blood pressure, blood glucose, smoking and prescription of an anti-platelet. Participants were followed to record incidence of myocardial infarction, stroke and cardiovascular death (MACE). The association of PAD-medical score with MACE was assessed using Cox propor-

Townsville Hospital Health Service human research ethics committees (HREC/13/QTHS/125 and HREC/14/QTHS/203).

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tional hazard analyses adjusting for age, sex and prior history of ischemic heart disease and stroke.

RESULTS

Between 2002 and 2020, a total of 424 participants with carotid artery disease ($n = 63$), aortic or peripheral aneurysm ($n = 121$) or lower limb ischemia ($n = 240$) were prospectively recruited, and followed for a median duration (inter-quartile range) of 2.0 (0.2–4.4) years. Only 33 (7.8%) participants had the optimal PAD-medical score of five, with 318 (75%) scoring at least three out of five. There were 89 (21.0%) participants that had at least one MACE during the follow-up period. A one-unit higher PAD-medical score was associated with lower risk of MACE (HR = 0.79, 95%CI: 0.63–0.98) after adjusting for other risk factors.

CONCLUSION

The PAD-medical score provides a simple way to assess the control of modifiable risk factors targeted by medical management aimed to reduce the incidence of MACE.

Key Words: Peripheral artery disease; Diabetes; Major cardiovascular events; Medical management; Prospective study; Clinical practice

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Core Tip: The control of modifiable risk factors for major adverse cardiovascular events (MACE) is frequently poorly achieved in patients with peripheral artery disease (PAD). The PAD-medical score is an easy way to assess the control of modifiable risk factors. In the current study only 33 (7.8%) of the included participants had optimal control of risk factors evidenced by a maximum PAD-medical score. Adjusted analyses found that a one-unit higher PAD-medical score was associated with a significantly lower risk of MACE (HR = 0.79, 95%CI: 0.63–0.98).

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INTRODUCTION

Diseases of the aorta and its branches (peripheral artery disease; PAD) are a collection of chronic occlusive and aneurysmal diseases, such as carotid artery disease, abdominal aortic aneurysm and lower limb ischemia[1–4]. Depending on study entry criteria and testing, between 10% and 60% of people with PAD have been reported to have diabetes[5]. Poorly controlled diabetes, as estimated by high hemoglobin A1c (HbA1c) concentrations, has been associated with an increased risk of major adverse cardiovascular events (MACE; myocardial infarction, stroke or cardiovascular death) in people with PAD[6,7], with approximately 20% having events during short-term follow-up[8–13].

Randomised controlled trials have demonstrated that medical therapies that control key cardiovascular risk factors, such as reducing low density lipoprotein-cholesterol (LDL-c) concentrations[11,14], blood pressure[15] and blood glucose[16], and reducing the risk of thrombosis[17], are effective at substantially reducing the risk of MACE. In clinical practice, however these therapies are poorly implemented[5,8,18–20]. Prior studies have suggested that poor implementation of medical therapies are associated with a higher incidence of MACE, but are limited through largely focusing on assessing the control of individual risk factors, such as blood pressure or LDL-c alone [8,18,19]. A holistic assessment of implementation of medical therapies amongst people with PAD and diabetes would consider control of all key modifiable risk factors.

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The first aim of this study was to examine the implementation of all the key medical therapies in accordance with current clinical guidelines in a group of people that had both PAD and diabetes. This included achieving optimal control of serum LDL-c, systolic blood pressure, HbA1c, smoking abstinence and prescription of an anti-platelet medication[21-23]. This was measured through the introduction of a new algorithm, PAD-medical, designed to quantify the relative control of the key modifiable risk factors targeted by optimal medical management. Secondly, this study aimed to examine the association of implementation of these combined medical therapies, estimated by the relative control of modifiable risk factors using PAD-medical score, with the incidence of MACE, adjusted for other risk factors.

MATERIALS AND METHODS

Study design and participants

This investigation was designed as part of an ongoing prospective cohort study that commenced in 2002, and aimed to identify risk factors associated with PAD outcomes [24,25]. The current study included adult participants (≥ 18 years old) with a prior history of a diagnosis of both diabetes and PAD, presenting to the outpatient vascular services at The Townsville University Hospital, the Mater Hospital Townsville and The Royal Brisbane and Women's Hospital in Queensland, Australia. People presenting with carotid artery disease, an abdominal or peripheral aneurysm or lower limb PAD diagnosed by a vascular specialist were eligible as long as they had a prior diagnosis of diabetes based on documented medical records from previous visits[26, 27]. Participants presenting without diagnoses of both diseases were excluded.

Lower limb PAD was defined to include symptoms of leg or foot pain or tissue loss and absence of lower limb pulses, ankle-brachial index ≤ 0.9 or imaging evidence of a lower limb artery stenosis of $\geq 50\%$ or occlusion[24,25]. Abdominal aortic aneurysm (AAA) was diagnosed if the orthogonal maximum outer to outer infra-renal aortic wall diameter was ≥ 30 mm measured from ultrasound or computed tomographic angiography[24,25]. Peripheral aneurysms were defined to include common or internal iliac artery diameters ≥ 15 and ≥ 8 mm respectively, or femoral or popliteal artery diameters of ≥ 15 mm and ≥ 9 mm respectively, as previously described[28]. A significant carotid artery stenosis was defined as $\geq 50\%$ using Australian Society for Ultrasound in Medicine criteria[24,25]. Written informed consent was obtained from all participants upon entry into the study. The study was performed in accordance with the Helsinki declaration and ethical approval was granted from the James Cook University and Townsville Hospital Health Service human research ethics committees (HREC/13/QTHS/125 and HREC/14/QTHS/203).

Risk factors and assessment of medical management

The implementation of medical management was assessed using a composite measure, the PAD-medical score, which was developed for this study in order to assess the control of the key modifiable risk factors targeted to reduce the risk of MACE[5,8,18, 29-31]. This scoring tool was developed to address the lack of an existing tool which applies to all age groups, and includes the relevant medical risk factors for people with concomitant PAD and diabetes (*e.g.*, HbA1c). The PAD-medical has a possible score of between 0 and 5, with zero indicating worst implementation of medical management and five indicating best implementation of medical management.

PAD-medical was calculated based on the control of key risk factors, smoking history and anti-platelet prescription measured at study entry. PAD-medical used risk factor targets for preventing MACE in patients with PAD indicated by current clinical guidelines[21-23], with each target achieved scoring one point. Values for some risk factors indicating partial control were scored either 0.25 or 0.5 points. The PAD-medical score was thus calculated as follows: Serum LDL-C: ≥ 3.0 mmol/L = 0, 2.5-2.9 mmol/L = 0.25; 1.8-2.4 mmol/L = 0.5; < 1.8 mmol/L = 1; Systolic blood pressure: > 160 mmHg = 0; 140-160 mmHg = 0.5; < 140 mmHg = 1; HbA1c: $> 9\%$ = 0; 7%-9% = 0.5; $< 7\%$ = 1; Smoking history: not smoked within the last month = 1; smoked within the last month = 0; Prescribed an anti-platelet medication: confirmed receiving = 1; not receiving = 0.

Definition and assessment of outcomes

At entry, participants underwent fasting blood tests, resting blood pressure was measured using an Omron Intellisense (HEM-907) monitor and smoking history and prescribed medications were recorded[8]. All prescribed medications including

antiplatelet drugs, statins and diabetes medications were recorded. Serum LDL-C, HbA1c and C-reactive protein were measured as previously described[27,32]. Ischemic heart disease (IHD) was defined as a history of myocardial infarction, angina or previous treatment for IHD[33].

Participants were offered follow up annually as part of standard care, and outpatient follow up was performed according to local clinical practice. Outcome data were recorded during clinical reviews on prospectively defined case report forms. Hospital charts and electronic records were also reviewed by a vascular specialist. Outcome data were also obtained from linked hospital admission records as previously described[24,25,34,35]. Linked data were obtained from the Queensland Hospital Admitted Patient Data Collection (QHAPDC) which is regularly audited to minimize inaccuracies[36]. The primary outcome was MACE, defined as the first occurrence of a major cardiovascular event including myocardial infarction, stroke or cardiovascular death.

Sample size

It was aimed to have adequate power to test the hypothesis that the PAD-medical score was associated with the risk of MACE. Previous studies suggest that approximately 30% of people with PAD have a MACE during short term follow-up[8,9,34]. Monte-Carlo simulations suggest that a multivariable regression model is powered sufficiently when 10 outcome events per degree of freedom of the predictor variables are observed[37]. Assuming an incidence of MACE of 20% to 30%, and planning to adjust for PAD-medical score (a composite of five risk factors), age, sex, IHD and stroke in the regression models, it was estimated that a sample size of over 400 participants would have adequate power to test the main hypothesis.

Statistical analysis

Data were analysed using the SPSS v25 (IBM, Armonk, NY, United States) software package. Continuous data that were not normally distributed, as confirmed using the Shapiro Wilk test, were presented as median and inter-quartile range (IQR). Between-group comparisons were conducted using the Mann-Whitney *U* and Kruskal-Wallis tests. Categorical variables were compared using Pearson's χ^2 test. Cox proportional hazard analyses assessed the association of PAD-medical score (one unit increase) with MACE adjusted for age, sex, smoking, IHD and prior stroke. Results were presented as hazard ratios (HR) and 95% confidence intervals (CI). *P* values of < 0.05 were accepted to be significant for all of these analyses.

RESULTS

Participants and implementation of medical management

Between February 2002 and August 2020, 424 participants with comorbid diabetes and PAD presenting with carotid artery disease (*n* = 63), aortic or peripheral aneurysm (*n* = 121) or lower limb ischemia (*n* = 240) were recruited. Only 33 (7.8%) of the participants had the optimal PAD-medical score of 5, with 173 (40.8%) scoring ≥ 4 , and 318 (75.0%) scoring ≥ 3 . Sex, age and history of IHD varied significantly between participants with different PAD-medical scores (Table 1). As expected, participants with the higher PAD-medical scores had significantly lower HbA1c, LDL-c and systolic blood pressure, reduced frequency of current smoking, and more frequent prescription of anti-platelet and statin medications (Table 2).

Association of PAD-medical score with MACE

Participants were followed for a median of 2.0 (0.2-4.4) years. During this time, 89 (21.0%) participants had at least one MACE. Overall, 43 participants had a myocardial infarction, 20 had a stroke and 51 a cardiovascular-related death, with 27 participants having multiple events. In unadjusted analyses, there was no relationship between MACE and PAD-medical score per unit increase (HR = 0.90, 95%CI: 0.73-1.11). In analyses adjusted for age, sex, IHD and stroke (Table 3), higher PAD-medical scores were associated with a significantly lower risk of MACE per unit increase (HR = 0.79, 95%CI: 0.63-0.98). Of the components of the PAD-medical score only smoking abstinence was significantly associated with a lower risk of MACE per unit increase (HR = 0.61, 95%CI: 0.38-0.97).

Table 1 Characteristics of include participants (*n* = 424)

Characteristic	Value
Age (median years, IQR)	69 (63-76)
Gender (male, %)	311 (73.3)
Aboriginal or Torres strait islander, <i>n</i> (%)	19 (4.5)
Presenting problem, <i>n</i> (%)	
Carotid artery disease	63 (14.9)
Aortic or peripheral aneurysm	121 (28.5)
Lower limb ischemia	240 (56.6)
Smoking status, <i>n</i> (%)	
Current	101 (23.8)
Former	211 (49.8)
Never	111 (26.2)
Missing	1 (0.2)
Medications, <i>n</i> (%)	
Aspirin	278 (65.6)
Other anti-platelet	84 (19.8)
Statins	324 (76.4)
Metformin	251 (59.2)
Other oral hypoglycemics	154 (36.3)
Insulin	98 (23.1)
Co-morbidities, <i>n</i> (%)	
Ischemic heart disease (IHD)	201 (47.4)
Stroke	47 (11.1)
Vitals (median, IQR)	
Glycated hemoglobin (HbA1c) (%)	6.9 (6.2-7.8)
Low-density lipoprotein (LDL)-c (mmol/L)	2 (1.5-2.6)
Systolic blood pressure (mmHg)	139 (125-151)
C-reactive protein (mg/L) ¹	2.7 (1.0-6.0)

¹C-reactive protein data is missing from 37 participants.

DISCUSSION

This study illustrates the considerable rate of clinically-important events in people that have PAD and diabetes, with 21% having at least one MACE during a median follow-up of 2 years. The main finding of the study was that most people with diabetes and PAD do not have optimal control of modifiable risk factors for MACE. Participants with better implementation of medical management, as identified by higher PAD-medical scores, had a lower of risk of MACE after adjusting for other risk factors. However, in sub-analyses, only smoking abstinence was found to be associated with a significantly reduced risk of MACE. The findings emphasize the need for methods to better implement medical management in people with PAD, particularly smoking cessation. The study also introduces a simple to use way to measure the overall success of control of modifiable risk factors using PAD-medical.

Previous studies show that people presenting with PAD have a higher risk of MACE than those frequently considered to be at the highest risk, such as those who have had a myocardial infarction or stroke[11]. Thus there is a need to develop strategies that improve the implementation of evidence-based medical therapies that are effective at reducing the incidence of MACE in people with PAD. Strategies to

Table 2 Association of peripheral artery disease-medical score with baseline characteristics

Risk factors	PAD-medical score				P value
	< 3.0 (n = 106)	3-3.9 (n = 145)	4.0-4.9 (n = 140)	5.0 (n = 33)	
Age	65 (57-73)	70 (64-77)	69 (64-77)	70 (66-76)	0.002 ^b
Male sex	67 (63.2)	110 (75.9)	110 (78.6)	24 (72.7)	0.046 ^a
Aboriginal or Torres Strait Islander	3 (2.8)	9 (6.2)	4 (2.9)	3 (9.1)	0.242
Presenting problem					0.043 ^a
Carotid artery disease	12 (11.3)	19 (13.1)	27 (19.3)	5 (15.2)	
Aortic or peripheral aneurysm	22 (20.8)	45 (31.0)	42 (30.0)	12 (36.4)	
Lower limb ischemia	72 (67.9)	81 (55.9)	71 (50.7)	16 (48.5)	
Smoking status					< 0.001 ^c
Current	55 (51.9)	41 (28.3)	5 (3.6)	0	
Former	28 (26.4)	62 (42.8)	100 (71.4)	21 (63.6)	
Never	22 (20.8)	42 (29.0)	35 (25.0)	12 (36.4)	
IHD	38 (35.8)	64 (44.1)	75 (53.6)	24 (72.7)	0.001 ^b
Stroke	14 (13.2)	12 (8.3)	17 (12.1)	4 (12.1)	0.606
Medications					
Aspirin	34 (32.1)	96 (66.2)	118 (84.3)	30 (90.9)	< 0.001 ^c
Other anti-platelet	11 (10.4)	25 (17.2)	41 (29.3)	7 (21.2)	0.002 ^b
Statins	58 (54.7)	115 (79.3)	121 (86.4)	30 (90.9)	< 0.001 ^c
Metformin	60 (56.6)	87 (60.0)	83 (59.3)	21 (63.6)	0.896
Other oral hypoglycemics	39 (36.8)	58 (40.0)	45 (32.1)	12 (36.4)	0.591
Insulin	26 (24.5)	35 (24.1)	33 (23.6)	4 (12.1)	0.482
HbA1c (%)	7.4 (6.8-8.7)	7.0 (6.5-7.7)	6.6 (6.0-7.6)	6.1 (5.9-6.4)	< 0.001 ^c
HDL-c (mmol/L)	1.1 (0.9-1.3)	1.1(0.9-1.3)	1.1(0.9-1.2)	0.9(0.8-1.2)	0.133
LDL-c (mmol/L)	2.60 (2.20-3.40)	2.10 (1.70-2.70)	1.60 (1.30-2.00)	1.34 (1.20-1.60)	< 0.001 ^c
SBP (mmHg)	150 (139-163)	139 (125-151)	135 (122-150)	126 (120-131)	< 0.001 ^c
C-reactive protein (mg/L)	3.0 (1.9-7.5) ¹	2.0 (1.0-5.0) ²	3.0 (1.0-5.6) ³	2.1 (0.9-5.0) ⁴	0.082
Major cardiovascular events	23 (21.7)	27 (18.6)	32 (22.9)	7 (21.2)	0.845

^aP < 0.05.^bP < 0.01.^cP < 0.001.

Data are presented as number (percentage) or median (interquartile range). C-reactive protein data is missing from 9¹, 15², 8³ and 5⁴ participants. PAD: Peripheral artery disease; IHD: Ischemic heart disease; HbA1c: Hemoglobin A1c; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; SBP: Systolic blood pressure.

promote smoking abstinence in particular may be of highest priority given its association with a reduced risk of MACE in this study. It is however currently unclear as to what intervention strategies would be effective in achieving better implementation of these measures amongst people with PAD. Possible strategies include physician and patient education programs and technology-enabled reminder systems for medications adherence [19,38]. In order to test such interventions and their contribution to achieving optimal medical management, there is a need for a simple scoring system to assess overall risk factor control which PAD-medical can provide.

Several models have been designed for predicting the incidence of MACE, such as the Framingham risk score, however these were mainly developed for use in primary rather than secondary prevention. The SMART-REACH model was developed for use in assessment of risk amongst people with established cardiovascular disease and has

Table 3 Association of peripheral artery disease-medical score and components with risk of major adverse cardiovascular events

Risk factor measure	HR	95%CI	P value
PAD-medical score	0.79	0.63 to 0.98	0.030 ^a
LDL-C score	0.80	0.46 to 1.39	0.436
HbA1c score	0.94	0.48 to 1.83	0.853
Blood pressure score	0.59	0.30 to 1.16	0.125
Smoking abstinence	0.61	0.38 to 0.97	0.036 ^a
Any anti-platelet	0.81	0.49 to 1.34	0.411

^aP < 0.05. Adjusted for age, sex, ischemic heart disease and stroke. PAD: Peripheral artery disease; LDL: Low-density lipoprotein; HbA1c: Hemoglobin A1c.

been used to model risk of MACE amongst people with PAD[39]. The SMART-REACH model, however, has a number of weaknesses in the assessment of the implementation of optimal medical management. These include the incorporation of risk factors not impacted by medical management, like age and sex, the lack of inclusion of key medical targets within the score calculation, such as HbA1c, and the ineligibility of some participants for the score, such as people older than 80 years. The PAD-medical score developed in this study aims to address these issues by strictly focusing on the medical management and risk factors targeted by medical management. As demonstrated in this study the PAD-medical score provides a convenient way to assess how well medical management is implemented, how modifiable risk factors are controlled and also the risk of MACE. The PAD-medical score may therefore be useful in the assessment of people with PAD.

The current study has a number of limitations that should be noted. Firstly, the sample size included was relatively small and recruited from one state in Australia. Secondly, a heterogeneous group of different PAD presentations was included. Thirdly, there was short median duration of participant follow-up. Fourthly, sub-analyses suggested a single risk factor (smoking abstinence) was associated with a lower risk of MACE. Finally, while the scoring system for PAD-medical was developed after considering current clinical guidelines targets[21-23], the cut-off values for the intermediate categories were set arbitrary. As a result of this and the small sample size, the findings of this study need to be validated in a more diverse population recruited from other localities, with a longer duration of follow-up.

CONCLUSION

This study illustrates the high incidence of clinically important events in people with PAD and diabetes. A simple-to-calculate score called PAD-medical is presented, which can be used to assess how well medical management therapy achieves control of modifiable risk factors. The PAD-medical score was predictive of the incidence of MACE during short-term follow-up.

ARTICLE HIGHLIGHTS

Research background

Peripheral artery disease is collection of chronic occlusive and aneurysmal diseases associated with a high incidence of major adverse cardiovascular events (MACE).

Research motivation

In this study, the control of modifiable risk factors for MACE was assessed through the development and testing of a new score called peripheral artery disease (PAD)-medical.

Research objectives

The aim of this study was to assess how the PAD-medical score, which assessed the control of modifiable risk factors was associated with the risk of MACE in people with

a diagnosis of both peripheral artery disease and diabetes.

Research methods

Patients with previously diagnosed peripheral artery disease and diabetes were recruited from three hospitals in Queensland Australia. PAD-medical score was calculated as a result from zero (worst management) to five (best management) based on the control of modifiable risk factors and implementation of medical management. Cox proportional hazard analyses assessed the association of PAD-medical score (one unit increase) with MACE adjusted for age, sex, smoking, IHD and prior stroke.

Research results

Of 424 participants recruited less than 10% had optimal control of modifiable risk factors evidenced by a top PAD-medical score. A one-unit increase in PAD-medical was associated with a significantly lower risk of MACE after adjusting for other risk factors (HR = 0.79, 95%CI: 0.63-0.98). Of the five different components of PAD-medical, only smoking abstinence was independently associated with a reduced risk of MACE (HR = 0.61, 95%CI: 0.38-0.97).

Research conclusions

The PAD-medical score represents an easy to use tool for the quantification of the control of modifiable risk factors for MACE in patients with peripheral artery disease and diabetes.

Research perspectives

Further research into this field requires a larger participant cohort from a more diverse population to investigate the wider applicability of the PAD-medical score.

REFERENCES

- 1 **Fowkes FG**, Aboyans V, Fowkes FJ, McDermott MM, Sampson UK, Criqui MH. Peripheral artery disease: epidemiology and global perspectives. *Nat Rev Cardiol* 2017; **14**: 156-170 [PMID: [27853158](#) DOI: [10.1038/nrcardio.2016.179](#)]
- 2 **Fowkes FG**, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, Norman PE, Sampson UK, Williams LJ, Mensah GA, Criqui MH. 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**: 1329-1340 [PMID: [23915883](#) DOI: [10.1016/S0140-6736\(13\)61249-0](#)]
- 3 **Sampson UK**, Norman PE, Fowkes FG, Aboyans V, Yanna Song, Harrell FE Jr, Forouzanfar MH, Naghavi M, Denenberg JO, McDermott MM, Criqui MH, Mensah GA, Ezzati M, Murray C. Global and regional burden of aortic dissection and aneurysms: mortality trends in 21 world regions, 1990 to 2010. *Glob Heart* 2014; **9**: 171-180.e10 [PMID: [25432126](#) DOI: [10.1016/j.ghart.2013.12.010](#)]
- 4 **Golledge J**. Lower-limb arterial disease. *Lancet* 1997; **350**: 1459-1465 [PMID: [9371181](#) DOI: [10.1016/S0140-6736\(97\)07421-7](#)]
- 5 **Nastasi DR**, Smith JR, Moxon JV, Trollope A, Golledge J. Prescription of Pharmacotherapy and the Incidence of Stroke in Patients With Symptoms of Peripheral Artery Disease. *Stroke* 2018; **49**: 2953-2960 [PMID: [30571405](#) DOI: [10.1161/STROKEAHA.118.022922](#)]
- 6 **Singh N**, Zeng C, Lewinger JP, Wolfson AM, Shavelle D, Weaver F, Garg PK. Preoperative hemoglobin A1c levels and increased risk of adverse limb events in diabetic patients undergoing infrainguinal lower extremity bypass surgery in the Vascular Quality Initiative. *J Vasc Surg* 2019; **70**: 1225-1234.e1 [PMID: [30852042](#) DOI: [10.1016/j.jvs.2018.12.041](#)]
- 7 **Low Wang CC**, Blomster JI, Heizer G, Berger JS, Baumgartner I, Fowkes FGR, Held P, Katona BG, Norgren L, Jones WS, Lopes RD, Olin JW, Rockhold FW, Mahaffey KW, Patel MR, Hiatt WR; EUCLID Trial Executive Committee and Investigators. Cardiovascular and Limb Outcomes in Patients With Diabetes and Peripheral Artery Disease: The EUCLID Trial. *J Am Coll Cardiol* 2018; **72**: 3274-3284 [PMID: [30573030](#) DOI: [10.1016/j.jacc.2018.09.078](#)]
- 8 **Thomas Manapurathe D**, Moxon JV, Krishna SM, Rowbotham S, Quigley F, Jenkins J, Bourke M, Bourke B, Jones RE, Golledge J. Cohort Study Examining the Association Between Blood Pressure and Cardiovascular Events in Patients With Peripheral Artery Disease. *J Am Heart Assoc* 2019; **8**: e010748 [PMID: [30845872](#) DOI: [10.1161/JAHA.118.010748](#)]
- 9 **Morris DR**, Skalina TA, Singh TP, Moxon JV, Golledge J. Association of Computed Tomographic Leg Muscle Characteristics With Lower Limb and Cardiovascular Events in Patients With Peripheral Artery Disease. *J Am Heart Assoc* 2018; **7**: e009943 [PMID: [30371256](#) DOI: [10.1161/JAHA.118.009943](#)]
- 10 **Bonaca MP**, Bhatt DL, Storey RF, Steg PG, Cohen M, Kuder J, Goodrich E, Nicolau JC, Parkhomenko A, López-Sendón J, Dellborg M, Dalby A, Špinar J, Aylward P, Corbalán R, Abola MTB, Jensen EC, Held P, Braunwald E, Sabatine MS. Ticagrelor for Prevention of Ischemic Events

- After Myocardial Infarction in Patients With Peripheral Artery Disease. *J Am Coll Cardiol* 2016; **67**: 2719-2728 [PMID: [27046162](#) DOI: [10.1016/j.jacc.2016.03.524](#)]
- 11 **Bonaca MP**, Nault P, Giugliano RP, Keech AC, Pineda AL, Kanevsky E, Kuder J, Murphy SA, Jukema JW, Lewis BS, Tokgozoglul, Somaratne R, Sever PS, Pedersen TR, Sabatine MS. 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**: 338-350 [PMID: [29133605](#) DOI: [10.1161/CIRCULATIONAHA.117.032235](#)]
 - 12 **Anand SS**, Caron F, Eikelboom JW, Bosch J, Dyal L, Aboyans V, Abola MT, Branch KRH, Keltai K, Bhatt DL, Verhamme P, Fox KAA, Cook-Bruns N, Lanius V, Connolly SJ, Yusuf S. Major Adverse Limb Events and Mortality in Patients With Peripheral Artery Disease: The COMPASS Trial. *J Am Coll Cardiol* 2018; **71**: 2306-2315 [PMID: [29540326](#) DOI: [10.1016/j.jacc.2018.03.008](#)]
 - 13 **Golledge J**, Moxon JV, Rowbotham S, Pinchbeck J, Yip L, Velu R, Quigley F, Jenkins J, Morris DR. Risk of major amputation in patients with intermittent claudication undergoing early revascularization. *Br J Surg* 2018; **105**: 699-708 [PMID: [29566427](#) DOI: [10.1002/bjs.10765](#)]
 - 14 **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**: 645-654; discussion 653 [PMID: [17398372](#) DOI: [10.1016/j.jvs.2006.12.054](#)]
 - 15 **Ostergren J**, Sleight P, Dagenais G, Danisa K, Bosch J, Qilong Y, Yusuf S; HOPE study investigators. Impact of ramipril in patients with evidence of clinical or subclinical peripheral arterial disease. *Eur Heart J* 2004; **25**: 17-24 [PMID: [14683738](#) DOI: [10.1016/j.ehj.2003.10.033](#)]
 - 16 **Goldman MP**, Clark CJ, Craven TE, Davis RP, Williams TK, Velazquez-Ramirez G, Hurie JB, Edwards MS. Effect of Intensive Glycemic Control on Risk of Lower Extremity Amputation. *J Am Coll Surg* 2018; **227**: 596-604 [PMID: [30336205](#) DOI: [10.1016/j.jamcollsurg.2018.09.021](#)]
 - 17 **Wong PF**, Chong LY, Mikhailidis DP, Robless P, Stansby G. Antiplatelet agents for intermittent claudication. *Cochrane Database Syst Rev* 2011; CD001272 [PMID: [22071801](#) DOI: [10.1002/14651858.CD001272.pub2](#)]
 - 18 **Nastasi DR**, Moxon JV, Norman R, Trollope AF, Rowbotham S, Quigley F, Jenkins J, Golledge J. The cost-effectiveness of intensive low-density lipoprotein cholesterol lowering in people with peripheral artery disease. *J Vasc Surg* 2021; **73**: 1396-1403.e3 [PMID: [32891803](#) DOI: [10.1016/j.jvs.2020.08.129](#)]
 - 19 **Burnier M**, Egan BM. Adherence in Hypertension. *Circ Res* 2019; **124**: 1124-1140 [PMID: [30920917](#) DOI: [10.1161/CIRCRESAHA.118.313220](#)]
 - 20 **World Health Organization**. Adherence to long-term therapies: evidence for action. 2003. Available from: https://www.who.int/chp/knowledge/publications/adherence_report/en/
 - 21 **Aboyans V**, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T, Collet JP, Czerny M, De Carlo M, Debus S, Espinola-Klein C, Kahan T, Kownator S, Mazzolai L, Naylor AR, Roffi M, Röther J, Sprynger M, Tendera M, Tepe G, Venermo M, Vlachopoulos C, Desormais I, Document Reviewers, Widimsky P, Kolh P, Agewall S, Bueno H, Coca A, De Borst GJ, Delgado V, Dick F, Erol C, Ferrini M, Kakkos S, Katus HA, Knuuti J, Lindholt J, Mattle H, Pieniazek P, Piepoli MF, Scheinert D, Sievert H, Simpson I, Sulzenko J, Tamargo J, Tokgozoglul, Torbicki A, Tsakountakis N, Tuñón J, Vega de Ceniga M, Windecker S, Zamorano JL. Editor's Choice - 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* 2018; **55**: 305-368 [PMID: [28851596](#) DOI: [10.1016/j.ejvs.2017.07.018](#)]
 - 22 **Gerhard-Herman MD**, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, Fleisher LA, Fowkes FGR, Hamburg NM, Kinlay S, Lookstein R, Misra S, Mureebe L, Olin JW, Patel RAG, Regensteiner JG, Schanzer A, Shishehbor MH, Stewart KJ, Treat-Jacobson D, Walsh ME. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2017; **69**: e71-e126 [PMID: [27851992](#) DOI: [10.1016/j.jacc.2016.11.007](#)]
 - 23 **Abola MTB**, Golledge J, Miyata T, Rha SW, Yan BP, Dy TC, Ganzon MSV, Handa PK, Harris S, Zhisheng J, Pinjala R, Robless PA, Yokoi H, Alajar EB, Bermudez-Delos Santos AA, Llanes EJB, Obrado-Nabablit GM, Pestaño NS, Punzalan FE, Tumanan-Mendoza B. Asia-Pacific Consensus Statement on the Management of Peripheral Artery Disease: A Report from the Asian Pacific Society of Atherosclerosis and Vascular Disease Asia-Pacific Peripheral Artery Disease Consensus Statement Project Committee. *J Atheroscler Thromb* 2020; **27**: 809-907 [PMID: [32624554](#) DOI: [10.5551/jat.53660](#)]
 - 24 **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**: 549-555 [PMID: [23742964](#) DOI: [10.1016/j.atherosclerosis.2013.04.030](#)]
 - 25 **Golledge J**, Ewels C, Muller R, Walker PJ. Association of chronic kidney disease categories defined with different formulae with major adverse events in patients with peripheral vascular disease. *Atherosclerosis* 2014; **232**: 289-297 [PMID: [24468141](#) DOI: [10.1016/j.atherosclerosis.2013.11.034](#)]
 - 26 **Parr A**, Buttner P, Shahzad A, Golledge J. Relation of infra-renal abdominal aortic calcific deposits and cardiovascular events in patients with peripheral artery disease. *Am J Cardiol* 2010; **105**: 895-899 [PMID: [20211340](#) DOI: [10.1016/j.amjcard.2009.10.067](#)]

- 27 **Golledge J**, Jayalath R, Oliver L, Parr A, Schurgers L, Clancy P. Relationship between CT anthropometric measurements, adipokines and abdominal aortic calcification. *Atherosclerosis* 2008; **197**: 428-434 [PMID: [17675038](#) DOI: [10.1016/j.atherosclerosis.2007.06.027](#)]
- 28 **Magee R**, Quigley F, McCann M, Buttner P, Golledge J. Growth and risk factors for expansion of dilated popliteal arteries. *Eur J Vasc Endovasc Surg* 2010; **39**: 606-611 [PMID: [20122854](#) DOI: [10.1016/j.ejvs.2009.12.031](#)]
- 29 **Golledge J**, Quigley F, Velu R, Walker PJ, Moxon JV. Association of impaired fasting glucose, diabetes and their management with the presentation and outcome of peripheral artery disease: a cohort study. *Cardiovasc Diabetol* 2014; **13**: 147 [PMID: [25361884](#) DOI: [10.1186/s12933-014-0147-2](#)]
- 30 **Harwood AE**, Smith GE, Cayton T, Broadbent E, Chetter IC. A Systematic Review of the Uptake and Adherence Rates to Supervised Exercise Programs in Patients with Intermittent Claudication. *Ann Vasc Surg* 2016; **34**: 280-289 [PMID: [27126713](#) DOI: [10.1016/j.avsg.2016.02.009](#)]
- 31 **Lin E**, Nguyen CH, Thomas SG. Completion and adherence rates to exercise interventions in intermittent claudication: Traditional exercise vs alternative exercise - a systematic review. *Eur J Prev Cardiol* 2019; **26**: 1625-1633 [PMID: [31216860](#) DOI: [10.1177/2047487319846997](#)]
- 32 **Moxon JV**, Ng E, Lazzaroni SM, Boulton M, Velu R, Fitridge RA, Golledge J. Circulating biomarkers are not associated with endoleaks after endovascular repair of abdominal aortic aneurysms. *J Vasc Surg* 2018; **67**: 770-777 [PMID: [28843790](#) DOI: [10.1016/j.jvs.2017.06.090](#)]
- 33 **Golledge J**, Leicht A, Crowther RG, Clancy P, Spinks WL, Quigley F. Association of obesity and metabolic syndrome with the severity and outcome of intermittent claudication. *J Vasc Surg* 2007; **45**: 40-46 [PMID: [17123770](#) DOI: [10.1016/j.jvs.2006.09.006](#)]
- 34 **Morris DR**, Singh TP, Moxon JV, Smith A, Stewart F, Jones RE, Golledge J. Assessment and validation of a novel angiographic scoring system for peripheral artery disease. *Br J Surg* 2017; **104**: 544-554 [PMID: [28140457](#) DOI: [10.1002/bjs.10460](#)]
- 35 **Moxon JV**, Jones RE, Wong G, Weir JM, Mellett NA, Kingwell BA, Meikle PJ, Golledge J. Baseline serum phosphatidylcholine plasmalogen concentrations are inversely associated with incident myocardial infarction in patients with mixed peripheral artery disease presentations. *Atherosclerosis* 2017; **263**: 301-308 [PMID: [28728066](#) DOI: [10.1016/j.atherosclerosis.2017.06.925](#)]
- 36 **Queensland Health**. Queensland hospital admitted data collection manual 2015-2016. Available from: <https://www.health.qld.gov.au/hsu/collections/qhapdc>
- 37 **Peduzzi P**, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol* 1996; **49**: 1373-1379 [PMID: [8970487](#) DOI: [10.1016/s0895-4356\(96\)00236-3](#)]
- 38 **Golledge J**, Fernando M, Lazzarini P, Najafi B, G Armstrong D. The Potential Role of Sensors, Wearables and Telehealth in the Remote Management of Diabetes-Related Foot Disease. *Sensors (Basel)* 2020; **20** [PMID: [32823514](#) DOI: [10.3390/s20164527](#)]
- 39 **Saratzis A**, Jaspers NEM, Gwilym B, Thomas O, Tsui A, Lefroy R, Parks M, Htun V, Mera Z, Thatcher A, Bosanquet D, Forsythe R, Benson R, Dattani N, Dovell G, Lane T, Shalhoub J, Sidloff D, Visseren FLJ, Dorresteijn JAN, Richards T; Vascular and Endovascular Research Network (VERN) Collaborators. Observational study of the medical management of patients with peripheral artery disease. *Br J Surg* 2019; **106**: 1168-1177 [PMID: [31259387](#) DOI: [10.1002/bjs.11214](#)]



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