Observational study of the medical management of patients with peripheral artery disease

A. Saratzis[1], N. E. M. Jaspers[3], B. Gwilym[2], O. Thomas[2], A. Tsui[2], R. Lefroy[2], M. Parks[2], V. Htun[2], Z. Mera[2], A. Thatcher[2], D. Bosanquet[2], R. Forsythe[2], R. Benson[2], N. Dattani[2], G. Dovell[2], T. Lane[2], J. Shalhoub[2], D. Sidloff[2], F. L. J. Visseren[3], J. A. N. Dorresteijn[3] and T. Richards[4], Vascular and Endovascular Research Network (VERN) Collaborators

[1]National Institute for Health Research Leicester Biomedical Research Centre, Leicester, and [2]Vascular and Endovascular Research Network, Birmingham, UK, [3]Department of Vascular Medicine, University Medical Centre Utrecht, Utrecht, the Netherlands, and [4]Department of Vascular Surgery University of Western Australia, Perth, Western Australia, Australia

Correspondence to: Mr A. Saratzis, National Institute for Health Research Leicester Biomedical Research Centre, British Heart Foundation Cardiovascular Research Facility (3rd floor), Leicester LE3 9QP, UK (e-mail: as875@le.ac.uk)

Background: Previous research has suggested that patients with peripheral artery disease (PAD) are not offered adequate risk factor modification, despite their high cardiovascular risk. The aim of this study was to assess the cardiovascular profiles of patients with PAD and quantify the survival benefits of target-based risk factor modification.

Methods: The Vascular and Endovascular Research Network (VERN) prospectively collected cardiovascular profiles of patients with PAD from ten UK vascular centres (April to June 2018) to assess practice against UK and European goal-directed best medical therapy guidelines. Risk and benefits of risk factor control were estimated using the SMART-REACH model, a validated cardiovascular prediction tool for patients with PAD.

Results: Some 440 patients (mean(s.d.) age 70(11) years, 24.8 per cent women) were included in the study. Mean(s.d.) cholesterol (4.3(1.2) mmol/l) and LDL-cholesterol (2.7(1.1) mmol/l) levels were above recommended targets; 319 patients (72.5 per cent) were hypertensive and 343 (78.0 per cent) were active smokers. Only 11.1 per cent of patients were prescribed high-dose statin therapy and 39.1 per cent an antithrombotic agent. The median calculated risk of a major cardiovascular event over 10 years was 53 (i.q.r. 44–62) per cent. Controlling all modifiable cardiovascular risk factors based on UK and European guidance targets (LDL-cholesterol less than 2 mmol/l, systolic BP under 140 mmHg, smoking cessation, antiplatelet therapy) would lead to an absolute risk reduction of the median 10-year cardiovascular risk by 29 (20–38) per cent with 6.3 (4.0–9.3) cardiovascular disease-free years gained.

Conclusion: The medical management of patients with PAD in this secondary care cohort was suboptimal. Controlling modifiable risk factors to guideline-based targets would confer significant patient benefit.

+A: Introduction

Peripheral artery disease (PAD) is an important health problem worldwide[1,2]. The prevalence of PAD has increased across all ages in the past 15 years[3]. All atherosclerotic diseases, including PAD, share common risk factors such as hyperlipidaemia, hypertension and smoking[2]. The presence of PAD is associated with a high risk of myocardial infarction, stroke and other cardiac events[1,2,4,5]; a patient with PAD is predicted to have a mortality rate six to eight times higher secondary to a major cardiovascular event within 10 years than that of age-matched patients without PAD[4,6]. Risk factor modification in this patient group is therefore important to reduce cardiovascular risk and need for intervention[4,7–9].

Hyperlipidaemia, hypertension, smoking and antithrombotic therapy are the main targets of risk factor control and best medical therapy in PAD[2]. A meta-analysis[10] reported that those with hyperlipidaemia were 20 per cent more likely to be diagnosed with PAD. Statin therapy in PAD reduces the risk of major cardiovascular events[11] and has been associated with reduced need for revascularization[12]. A meta-analysis[13] of BP control specifically in PAD has shown that achieving normotension improves both cardiovascular and PAD-specific outcomes, including need for intervention. A meta-analysis[14] has also reported that the magnitude of the association between smoking and PAD is greater than that reported in other atherosclerotic diseases. Finally, the benefits of antithrombotic therapy in this clinical setting are multiple; it reduces both limb interventions and future cardiovascular risk[15]. Clopidogrel conferred a 24 per cent relative risk reduction in terms of future cardiovascular events in PAD compared with aspirin in one trial[16] and is currently the preferred first-line treatment in the relevant UK guidance; the American Society for Vascular Surgery (SVS) guidance[17] also suggests clopidogrel as an alternative to aspirin for those with PAD.

National Institute for Health and Care Excellence (NICE; documents CG181 and CG147)[18,19], European Society of Cardiology (ESC)[20] and SVS[17] guidance highlight a series of interventions to address excess cardiovascular risk and potentially reduce the risk of limb loss. These guidelines list specific targets that should be achieved for each risk factor in order to gain the maximum potential benefits. Control of additional risk factors may provide incremental benefits.

The SMART-REACH (Secondary Manifestations of Arterial Disease–Reduction of Atherothrombosis for Continued Health) model[21,22] was developed and validated in the prospective SMART and REACH cohorts of patients with cardiovascular disease, and has been validated externally in several populations. Based on readily available individual

characteristics, the model estimates an individual's benefit from preventive strategies in terms of individual gain in life expectancy without recurrent cardiovascular events (cardiovascular disease-free life expectancy), and individual lifetime and 10-year absolute risk reduction (ARR)[22]. The SMART-REACH model can be used to direct intensive treatment and follow-up using specific lipid and BP targets, and may encourage patients to adhere to therapy.

The aim of this study was to compare the current risk factor management of patients with PAD in the UK against specific targets set by international guidance. Based on these individual-patient data, the future cardiovascular risk of these individuals was quantified and the potential benefits of goal-directed risk factor modification compared in terms of 10-year cardiovascular risk and cardiovascular disease-free life expectancy.

+A: Methods

Patients were identified prospectively by a member of the Vascular and Endovascular Research Network (VERN), a national collaborative group of research-active vascular healthcare professionals with access to several tertiary and district vascular surgery units across the UK[23]. One VERN member, a vascular surgery trainee, was responsible for identification of patients at each centre via weekly PAD clinics in the outpatient setting. All patients had been assessed in an outpatient clinic at least once previously by a vascular surgeon who established the primary diagnosis within 6 months. A total of ten VERN vascular units took part (based in England, Scotland and Wales), representing 14 per cent of the institutions that provide tertiary intervention for PAD in the UK, based on 2017 National Vascular Registry data[24]. At each vascular centre, one local VERN representative (a healthcare professional) was responsible for regulatory approvals, identification of patients and remote data upload using a secure electronic server. The project was registered before recruiting any patients as audit of clinical practice in each centre, and did not therefore

require global ethical approval, in accordance with current National Health Service (NHS) guidance. Data collected were anonymized and the project complied with the Declaration of Helsinki and NHS Caldicott principles[25].

Consecutive patients with any of the following primary diagnoses were eligible for inclusion: intermittent claudication, critical limb ischaemia (presence of ischaemic rest pain and/or tissue loss and/or ankle : brachial index below 0.4), atherosclerotic carotid artery disease (carotid artery stenosis depicted on cross-sectional arterial imaging) and/or aortic/peripheral artery aneurysm (aortic, iliac and/or popliteal artery aneurysm). The primary diagnosis had already been established by a vascular surgeon based on clinical examination and subsequent imaging during a previous visit to an outpatient clinic, or during a hospital stay, at least 6 months in advance. Lipid profiles were identified using each hospital's electronic patient records or by contacting the patient's general practitioner. Patients were not excluded simply on the basis of missing lipid-related information. All diagnoses and clinical events were defined according to the American Heart Association guidance for cardiovascular studies[26]. Electronic patient records, clinic notes, prescriptions and clinic letters were searched to identify missing information. Data were collected and registered prospectively between May 2018 and August 2018. BP measurements were performed immediately before review by the surgeon in clinic in a seated position using a validated electronic device in all patients (Omron 907 BP Monitor, Omron, Milton Keynes, UK; or General Electric GE Dinamap® Procare Series Vitals Monitor, General Electric, Chicago, Illinois, USA). Information relating to the patients' prescriptions were obtained using the letters from primacy care and latest patient prescription sheets.

+B: Standards of medical treatment

NICE (CG181 and CG147)[18,19] and ESC[20] standards on best medical therapy in PAD were used to define treatment goals for each patient. The recommendations of NICE and ESC are very similar to those of the SVS[17] for this population group (*Table 1*).

+B: Impact of risk factor control on cardiovascular risk

The SMART-REACH model was used to quantify cardiovascular risk and possible benefits if each risk factor was controlled based on contemporary clinical guidelines. SMART-REACH uses ten predictors: age, sex, current smoking (yes/no), diabetes mellitus (yes/no), systolic BP, total cholesterol, creatinine, number of locations of cardiovascular disease (coronary artery disease, PAD), history of atrial fibrillation (yes/no) and history of congestive heart failure (yes/no). Missing variables were handled by means of imputation using predictive mean matching (aregImpute, Hmisc package, R software; R Project for Statistical Computing, Vienna, Austria) and reported population frequencies and medians from REACH Western Europe[27]. The SMART-REACH model consists of two complementary competing-risk-adjusted left-truncated cause-specific hazard functions: one for cardiovascular events, and one for non-cardiovascular mortality. Therapy benefit can be estimated by combining the functions with hazard ratios (HRs) from published preventive therapy meta-analyses and trials. For the purpose of these analyses, the therapy benefit was expressed in terms of three different metrics: 10-year risk of cardiovascular events, with therapy benefit in terms of 10-year ARR; lifetime risk of cardiovascular events, defined as the risk of having an event before the 90th life-year, with therapy benefit in terms of lifetime ARR; and cardiovascular-free life expectancy, defined as median life expectancy without a cardiovascular event or death, with therapy benefit in terms of years gain in cardiovascular-free life expectancy.

The therapy benefits from four different treatment goals were estimated separately: lipid control, BP control, smoking cessation and antiplatelet therapy.

+C: Lipid-lowering goals

ESC guidelines[20] recommend therapy to achieve an LDL-cholesterol level of below1.8 mmol/l for patients at high cardiovascular risk. Based on published data, a 1.0-mmol reduction in LDL-cholesterol corresponds to a cardiovascular-specific HR of 0.78, from which a predicted ARR in future events was modelled using ideal LDL-cholesterol levels (below 1.8 mmol/l) based on the SMART-REACH model[28,29]. Patients who had already achieved the recommended LDL-cholesterol goal were modelled with a HR of 1.00.

+C: BP treatment goals

The target is to achieve a systolic BP of 140 mmHg; a 10-mmHg reduction in systolic BP corresponds to a cardiovascular-specific HR of 0.77[30]. Patients who had already achieved this goal were modelled with a HR of 1.00. An ARR in predicted future events was calculated using the SMART-REACH model.

+C: Smoking cessation

Smoking reduces the HR for both cardiovascular and non-cardiovascular mortality. The HR for cardiovascular events, based on published data, for current smokers *versus* ex-smokers is 0.60, derived from the HR of current smokers *versus* never smokers (HR 1.98) and ex-smokers *versus* never smokers (HR 1.18)[31]. The HR for non-vascular events for current smokers who are now ex-smokers is 0.73, derived from the HR of current smokers *versus* never smokers (HR 1.83) and ex-smokers *versus* never smokers (HR 1.34)[32].

+C: Antiplatelet therapy

Aspirin at a dose of 75 mg per day was used as the ideal antiplatelet therapy. The benefits of initiating aspirin (modelled only in those receiving no antithrombotic treatment) were

modelled based on published data[33], to calculate an ARR in predicted future events using the SMART-REACH model.

+C: Overall benefit

The overall benefit of achieving optimal control of all four modifiable factors was modelled and a relevant ARR calculated. The SMART-REACH model is available online (https://www.u-prevent.com/en-GB).

+B: Statistical analysis

Normality of distributions was assessed based on skewness, kurtosis and the Kolmogorov–Smirnov test. Continuous variables with a normal distribution are presented as mean (s.d.), and those with a non-normal distribution as median (i.q.r). Categorical data are presented as absolute value and corresponding percentage. Normally distributed continuous data were compared using Student's *t* test. Comparisons between categorical data were performed using χ^2 test. $P < 0.050$ was considered statistically significant. Quantitative analyses were done using SPSS® version 24.0 for Windows® (IBM, Armonk, New York, USA) or R version 1.0.143 for Windows®.

+A: Results

A total of 440 patients (mean(s.d.) age 70(11) years; 24.8 per cent women) were included, of whom 54.1 per cent had intermittent claudication, 25.7 per cent had critical limb ischaemia and 9.3 per cent had an abdominal aortic aneurysm. Some 48.2 per cent of the patients were hyperlipidaemic (based on lipid levels compared with NICE/ESC/SVS guidance), 65.9 per cent had high BP when they initially presented to secondary care, 78.0 per cent were current or ex-smokers and 32.5 per cent had a history of established ischaemic heart disease (*Table 2*). Thirty-two patients (7.3 per cent) had undergone intervention to treat PAD in the past.

+B: Standards of medical treatment

+C: Lipid targets, measurement and referral

Mean(s.d.) cholesterol levels were 4.3(1.2) mmol/l and mean LDL-cholesterol levels were 2.7(1.1) mmol/l; 43.6 per cent of patients had a cholesterol level of 4 mmol/l or higher and 45.2 per cent an LDL-cholesterol level of at least 1.8 mmol/l. There were seven individuals (1.6 per cent) with a total cholesterol level above 7.5 mmol/l and 117 (26.6 per cent) with an LDL-cholesterol level higher than 2.6 mmol/l. A total of 22 patients (5.0 per cent) had not had a total cholesterol test, and 108 (24.5 per cent) had not had LDL- and HDL-cholesterol levels measured after the diagnosis of PAD had been made.

+C: Statin prescribing for the prevention of cardiovascular disease (secondary prevention)

Overall, 337 patients (76.6 per cent) were prescribed a statin; 57.7 per cent were prescribed atorvastatin, 12.5 per cent simvastatin and 1.6 per cent pravastatin. A minority, 49 patients (11.1 per cent), were prescribed high-dose statin therapy (80 mg atorvastatin or an alternative high-dose statin) as defined and recommended by current NICE and ESC guidance. Those prescribed high-dose statin therapy did not have significantly lower lipid levels than those who were not (*Table 3*). Nor were they more likely to have a total cholesterol level below 4 mmol/l or an LDL-cholesterol level lower than 1.8 mmol/l (*Table 3*). The uptake of statin prescribing did not differ based on diagnosis ($P = 0.392$). Ten of 118 individuals who had already started on a statin at first presentation (8.5 per cent) were eligible for therapy using a monoclonal antibody targeting LDL such as evolocumab, based on current NICE guidance.

+C: BP control

A total of 319 patients (72.5 per cent) were hypertensive at baseline.

+C: Smoking cessation

Some 343 patients (78.0 per cent) were current smokers, and 93 (21.1 per cent) were ex-smokers (quit over a 1 year ago) or had never smoked.

+C: Antiplatelet therapy

There was a paucity of routine antiplatelet therapy; 84 patients (19.1 per cent) were prescribed 75 mg clopidogrel daily and 124 (28.2 per cent) 75 mg aspirin daily. Overall, 269 (61.1 per cent) had not been prescribed any antiplatelet or anticoagulant. The uptake of antiplatelet prescribing did not differ based on diagnosis ($P = 0.834$).

+B: Impact of risk factor control on cardiovascular risk

A total of 352 patients were aged between 45 and 80 years at baseline, and could thus have the benefit from therapy estimated using the SMART-REACH score. These patients had a median age of 68 (range 62–73 years) and 78.1 per cent were men. Median LDL-cholesterol was 2.6 (range 2.0–3.4) mmol/l, median systolic BP was 157 (range 129–175) mmHg, and 80.9 per cent were current smokers. The percentage of each variable handled by multiple imputation was: total cholesterol, 30.2 per cent; LDL, 44.6 per cent; current smoking, 0.59 per cent; sex, 0.29 per cent; diabetes, 0.29 per cent; cardiovascular event, 0.29 per cent; and age, 0.28 per cent. In line with the population statistics, the frequency of congestive heart failure was 15.1 per cent, that of atrial fibrillation was 11.1 per cent, and the median creatinine concentration was 92 μmol/l[29]. After imputation of missing variables, 272 patients (77.3 per cent) had an LDL-cholesterol level above 1.8 mmol/l and 261 (74.1 per cent) a systolic BP higher than 140 mmHg.

For the overall population, the 10-year risk of a cardiovascular event was 53 (i.q.r. 44–62) per cent, the lifetime risk of a cardiovascular event was 73 (68–78) per cent and the cardiovascular disease-free life expectancy was 74.6 (70.0–79.0) years with a mean of 6.4

(4.8–8.5) remaining cardiovascular disease-free years. The therapy benefits are summarized in *Fig. 1*, *Table 4*, and *Figs S1–S4* (supporting information).

The median therapy benefit from achieving an LDL-cholesterol level below 1.8 mmol/l (ESC guidance) is shown in *Fig. S1* (supporting information). For those with a baseline LDL-cholesterol level of 1.8 mmol/l or higher, there was a 7 per cent ARR in 10-year and a 6 per cent ARR in lifetime predicted cardiovascular events, with 1.0 cardiovascular disease-free years gained.

The median therapy benefit from achieving a systolic BP below 140 mmHg is shown in *Fig. S2* (supporting information). For those with a baseline SBP of 140 mmHg or higher, there was a 20 per cent ARR reduction in 10-year and a 19 per cent ARR in lifetime predicted cardiovascular events, with 3.3 cardiovascular disease-free years gained.

The median therapy benefit from smoking cessation is shown in *Fig. S3* (supporting information). For those who were smokers at baseline, smoking cessation led to a 14 per cent ARR reduction in 10-year and an 8 per cent reduction in lifetime predicted cardiovascular events, with 2.9 cardiovascular disease-free years gained.

The median therapy benefit from aspirin-equivalent antithrombotic therapy is shown in *Fig. S4* (supporting information). Initiating 75 mg a day aspirin would result in a 7 per cent ARR in 10-year predicted events, with 0.9 cardiovascular disease-free years gained.

Controlling all modifiable risk factors in accordance with NICE/ESC guidance, including LDL-cholesterol levels, systolic BP, stopping smoking and taking an antiplatelet, would confer a 29 per cent ARR in predicted 10-year cardiovascular events, with 6.3 cardiovascular disease-free years gained. This means that the residual risk following successful implementation of NICE/ESC guidance in all patients would be as follows: 21 (i.q.r. 13–29) per cent absolute risk of 10-year cardiovascular events, 42 (31–54) per cent

absolute risk of lifetime cardiovascular events, and 82 (77–85) years of cardiovascular disease-free life expectancy.

+A: Discussion

In this study of ten vascular centres in the UK the medical management of patients with PAD was suboptimal. Previous studies[34,35] by VERN in the UK had highlighted that cardiovascular risk management in patients with aneurysms is suboptimal. Most patients in the present series were hyperlipidaemic and hypertensive. Many patients were still smoking, even though they had already been seen in secondary care regarding their PAD. Furthermore, the adoption of antiplatelet prescribing was poor. There was significant variation in therapy benefit from lipid-lowering, BP-lowering and antiplatelet therapy, and smoking cessation estimated using the externally validated SMART-REACH lifetime model. The median gain in cardiovascular disease-free life expectancy from therapies ranged from 1.0 life-years for additional lipid-lowering therapy to 6.3 life-years for all therapies combined. Overall, these data have important implications for clinical practice; controlling these modifiable risk factors has the potential to achieve great reductions in cardiovascular events and mortality.

Lipid and BP control, smoking cessation and antiplatelet therapy are the main constituents of modifiable risk factor control in PAD[2]. The Heart Protection Study[36] reported that treatment with simvastatin reduced the rate of major vascular events by about one-quarter in patients with PAD, independent of the baseline cholesterol level, and also reduced the rate of limb events by 16 per cent. A Cochrane meta-analysis[37] of 17 lipid-lowering trials reported a 26 per cent reduction in cardiovascular events among patients with PAD treated with statins; the maximum benefits were seen in those with a higher baseline total cholesterol concentration. The randomized FOURIER trial[7] of a monoclonal antibody (evolocumab) which targets LDL showed that aggressive LDL lowering leads to a significant reduction in

cardiovascular events among patients with PAD. Only 11.1 per cent of the population in the present analysis was prescribed high-intensity statin therapy, which was reflected in the subsequent lipid profiles, with mean levels of both total cholesterol and LDL-cholesterol exceeding the recommended normal values based on NICE and ESC guidance. Prescribing high-intensity statin therapy was not significantly associated with lower levels of total cholesterol or LDL-cholesterol in this study. This may be partly due to a type II error; however, it also provides evidence that personalized medicine protocols with specific lipid targets may be of benefit in this population, rather than a blanket policy of offering everyone the same type of lipid-lowering medication.

The overall benefits of normal BP in terms of cardiovascular prevention are well established in anyone who is at increased risk. A meta-analysis[13] of BP control specifically in patients with PAD has shown that BP control improves PAD-specific outcomes as well as future cardiovascular risk. Similar to BP control, smoking cessation in patients with cardiovascular disease is very important. Interestingly, a meta-analysis[14] has reported that the magnitude of the association between smoking and PAD is greater than that reported for other atherosclerotic diseases, which further supports the importance of smoking cessation in this specific population. As far as antiplatelets are concerned, the pivotal CAPRIE trial[16] assessed the efficacy of clopidogrel (75 mg once daily) *versus* aspirin in reducing the risk of a composite outcome consisting of ischaemic stroke, myocardial infarction or vascular death. There was an all-group relative risk reduction of 8.7 per cent in favour of clopidogrel. The relative risk reduction in the PAD subgroup was even more significant at 23.8 per cent, in favour of clopidogrel[16]. Current NICE guidance supports offering 75 mg clopidogrel daily to patients with established PAD, unless contraindicated, in which case 75 mg aspirin is the preferred choice. In the present series, BP control was poor, and so was the uptake of smoking cessation and antiplatelet prescribing. Further to providing a description of the

current medical management of patients with PAD in the UK, this research also attempted to quantify the overall cardiovascular risk reduction in this specific patient group, had risk factors been controlled in accordance with NICE and ESC guidance. Quantifying cardiovascular risk in such populations is challenging, given that traditional widely used risk prediction tools (such as Framingham risk score or Q-risk) have not been developed for use in patients with existing cardiovascular disease or PAD. A novel externally validated model, the REACH-SMART score, was therefore used, which has been designed specifically for use in individuals with established cardiovascular disease[22]. Significant reductions in 10-year predicted morbidity and mortality would have been achieved had lipids and BP been controlled within recommended values. Most importantly, controlling all four of the modifiable risk factors addressed in this series would confer a 29 per cent ARR in predicted 10-year cardiovascular events, with 6.3 years of cardiovascular disease-free survival gained.

Any recommendations regarding how primary and secondary care can improve the treatment of these individuals should be based on findings from high-quality qualitative research involving patients, their carers, nurses and clinicians from both primary- and secondary-care settings. Previous research in similar settings has suggested several community-based interventions; however, there is lack of evidence specifically for patients with PAD.

This analysis has some limitations that need to be considered. In-depth analyses cannot be performed to assess interactions between clinical presentations and lipid levels or type of medication(s) prescribed given the size of this cohort. Furthermore, the present audit is cross-sectional, and lipid levels before and after statin therapy had been initiated could not be compared. Furthermore, the overall duration of statin therapy in this group could not be established. Despite the prospective nature of the audit, some data had to be collected retrospectively (missing information). Patients on high-dose statin therapy in this series did

not appear to have significantly lower lipid levels. This may be partly due to a type II error; despite the multicentre nature of this project, collecting accurate and up-to-date lipid profiles is laborious and hence the overall size of the population analysed was fairly limited. Other factors such as duration of therapy may also play a role; however, it was not possible to explore such associations in this cross-sectional analysis. The value of statins has been established in several high-quality randomized trials and statin therapy should remain an integral part of medical therapy in this population. This project was not designed to detect differences specifically relating to the intensity of statin therapy. Another limitation of this project relates to adherence by patients. The design of this research did not allow the investigators to monitor or test adherence to medication or any other intervention by the patients. The participants were asked whether they had been prescribed the medication during clinic appointments and their prescriptions/notes were reviewed. No further action was taken to inquire regarding adherence.

+A: Acknowledgements

This research was funded partly by Amgen. None of the investigators received reimbursements or financial incentives.

Disclosure: The authors declare no conflict of interest.

+A: References

1 <B>Sampson UKA, Fowkes FGR, Naidoo NG, Criqui MH. Peripheral artery disease. In *Cardiovascular, Respiratory, and Related Disorders* (3rd edn), Prabhakaran D, Anand S, Gaziano TA, Mbanya JC, Wu Y, Nugent R (eds). International Bank for Reconstruction and Development/The World Bank: Washington, 2017.

2 Morley RL, Sharma A, Horsch AD, Hinchliffe RJ. Peripheral artery disease. *BMJ* 2018; **360**: j5842.

3 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.

4 Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ *et al.* Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* 1992; **326**: 381–386.

5 Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. *Circ Res* 2015; **116**: 1509–1526.

6 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**: 176–184.

7 Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA *et al.*; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017; **376**: 1713–1722.

8 Rajamani K, Colman PG, Li LP, Best JD, Voysey M, D'Emden MC *et al.*; FIELD study investigators. Effect of fenofibrate on amputation events in people with type 2 diabetes mellitus (FIELD study): a prespecified analysis of a randomised controlled trial. *Lancet* 2009; **373**: 1780–1788.

9 Bailey MA, Dunne JA, Griffin KJ, Coughlin PA, Scott DJ. Systematic review and meta-analysis of the effects of statin therapy on abdominal aortic aneurysms (*Br J Surg* 2011; **98**: 362–353). *Br J Surg* 2011; **98**: 744–745.

10 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**: 1329–1340.

11 Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L *et al.* Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet* 2016; **388**: 2532–2561.

12 Navarese EP, Robinson JG, Kowalewski M, Kolodziejczak M, Andreotti F, Bliden K *et al.* Association between baseline LDL-C level and total and cardiovascular mortality after LDL-C lowering: a systematic review and meta-analysis. *JAMA* 2018; **319**: 1566–1579.

13 Thomas Manapurathe D, Krishna SM, Dewdney B, Moxon JV, Biros E, Golledge J. Effect of blood pressure lowering medications on leg ischemia in peripheral artery disease patients: a meta-analysis of randomised controlled trials. *PLoS One* 2017; **12**: e0178713.

14 Lu L, Mackay DF, Pell JP. Meta-analysis of the association between cigarette smoking and peripheral arterial disease. *Heart* 2014; **100**: 414–423.

15 Katsanos K, Spiliopoulos S, Saha P, Diamantopoulos A, Karunanithy N, Krokidis M *et al.* Comparative efficacy and safety of different antiplatelet agents for prevention of major cardiovascular events and leg amputations in patients with peripheral arterial disease: a systematic review and network meta-analysis. *PLoS One* 2015; **10**: e0135692.

16 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**: 1329–1339.

17 Society for Vascular Surgery Lower Extremity Guidelines Writing Group, Conte MS, Pomposelli FB, Clair DG, Geraghty PJ, McKinsey JF *et al.*; Society for Vascular Surgery. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. *J Vasc Surg* 2015; **61**(Suppl): 2S–41S.

18 Layden J, Michaels J, Bermingham S, Higgins B; Guideline Development Group. Diagnosis and management of lower limb peripheral arterial disease: summary of NICE guidance. *BMJ* 2012; **345**: e4947.

19 <B>National Clinical Guideline Centre (UK). *Lipid Modification: Cardiovascular Risk Assessment and the Modification of Blood Lipids for the Primary and Secondary Prevention of Cardiovascular Disease*. National Institute for Health and Care Excellence: London, 2014.

20 Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL *et al.*; ESC Scientific Document Group. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016; **37**: 2315–2381.

21 <EPATH> European Society of Cardiology. *The SMART Risk Score*. https://www.escardio.org/Education/ESC-Prevention-of-CVD-Programme/Risk-assessment/SMART-Risk-Score [accessed 12 February 2019].

22 Kaasenbrood L, Bhatt DL, Dorresteijn JAN, Wilson PWF, D'Agostino RB Sr, Massaro JM *et al.* Estimated life expectancy without recurrent cardiovascular events

in patients with vascular disease: the SMART-REACH Model. *J Am Heart Assoc* 2018; **7**: e009217.

23 Bosanquet DC; Vascular and Endovascular Research Network (VERN) Committee. How to engage in trainee-led multicentre collaborative vascular research: the Vascular and Endovascular Research Network (VERN). *Eur J Vasc Endovasc Surg* 2016; **52**: 392.

24 <EPATH> Vascular Services Quality Improvement Programme. *National Vascular Registry Report 2017*. https://www.vsqip.org.uk/reports/2017-annual-report/ [accessed 25 May 2019].

25 Greenough A, Graham H. Protecting and using patient information: the role of the Caldicott Guardian. *Clin Med (Lond)* 2004; **4**: 246–249.

26 Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A *et al.*; ACC/AHA Task Force on Clinical Data Standards Members. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association task force on clinical data standards (writing committee to develop cardiovascular endpoints data standards). *Circulation* 2015; **132**: 302–361.

27 Kaasenbrood L, Bhatt DL, Dorresteijn JAN, Wilson PWF, D'Agostino RB Sr, Massaro JM *et al.* Estimated life expectancy without recurrent cardiovascular events in patients with vascular disease: the SMART-REACH model. *J Am Heart Assoc* 2018; **7**: e009217.

28 Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009; **338**: b1665.

29 Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C *et al.* 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**: 1670–1681.

30 Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J *et al.* Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016; **387**: 957–967.

31 Mons U, Müezzinler A, Gellert C, Schöttker B, Abnet CC, Bobak M *et al.*; CHANCES Consortium. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. *BMJ* 2015; **350**: h1551.

32 Gellert C, Schöttker B, Brenner H. Smoking and all-cause mortality in older people: systematic review and meta-analysis. *Arch Intern Med* 2012; **172**: 837–844.

33 Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J *et al.* Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009; **373**: 1849–1860.

34 Saratzis A, Dattani N, Brown A, Shalhoub J, Bosanquet D, Sidloff D *et al.*; Vascular and Endovascular Research Network (VERN). Multi-centre study on cardiovascular risk management on patients undergoing AAA surveillance. *Eur J Vasc Endovasc Surg* 2017; **54**: 116–122.

35 Bath MF, Saratzis A, Saedon M, Sidloff D, Sayers R, Bown MJ; UKAGS investigators. Patients with small abdominal aortic aneurysm are at significant risk of cardiovascular events and this risk is not addressed sufficiently. *Eur J Vasc Endovasc Surg* 2017; **53**: 255–260.

36 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.

37 <JCIT>Aung PP, Maxwell HG, Jepson RG, Price JF, Leng GC. Lipid-lowering for peripheral arterial disease of the lower limb. *Cochrane Database Syst Rev* 2007; (4)CD000123.

Supporting information
Additional supporting information can be found online in the Supporting Information section at the end of the article.

Typesetter: please refer to marked-up figures

Fig. 1 Cardiovascular disease risk estimation based on the SMART-REACH model

Fig. 1 footnote: **a** Ten-year cardiovascular disease (CVD) risk, **b** lifetime CVD risk, **c** remaining CVD-free life-years and **d** prognosis and treatment benefit; values are median (i.q.r.). The analysis included 352 patients. Risk estimation is based on achieving optimal control of low-density lipoprotein, systolic BP, smoking status and antiplatelet therapy (with 75 mg aspirin daily); a predicted absolute risk reduction (ARR) is reported, based on the SMART-REACH model.

Table 1 Recommended standards of medical treatment	
Target	**Treatment and goal**
Lipid targets, measurement and referral	At presentation and before starting lipid modification therapy, measure HDL-cholesterol, LDL-cholesterol and total cholesterol to achieve the best estimate of CVD risk. A fasting sample is not needed. For individuals at high cardiovascular risk (which pertains to all individuals who have been diagnosed with PAD), lipid modification therapy should aim to achieve an LDL-cholesterol level below 1.8 mmol/l.
Statin prescribing for prevention of CVD (secondary prevention)	Start statin treatment with 80 mg atorvastatin (or an alternative statin using the highest recommended dose)
BP control	Offer medication aiming to achieve a BP of less than 140/90 mmHg
Smoking cessation	Offer all current smokers medication and referral to appropriate services to support smoking cessation
Antiplatelet therapy	Clopidogrel 75 mg daily is the preferred antiplatelet medication for those with PAD. If clopidogrel is contraindicated or not tolerated, offer low-dose aspirin alone (the SVS suggests 75 mg aspirin as first-line therapy, but also comments that 75 mg clopidogrel is supported by level 1 evidence and recommends it as an alternative)

HDL, high-density lipoprotein; LDL, low-density lipoprotein; CVD, cardiovascular disease; PAD, peripheral artery disease; SVS, American Society for Vascular Surgery.

Table 2 Baseline characteristics of interest	
	No. of patients* (*n* = 440)
Demographics	
Age (years)*	70(11)
Sex ratio (M : F)	331 : 109
Baseline diagnosis	
Intermittent claudication	238 (54.1)
Abdominal aortic aneurysm	41 (9.3)
Critical lower limb ischaemia	113 (25.7)
Mixed lower limb ulcer	18 (4.1)
Carotid artery disease	10 (2.3)
Other	20 (4.5)
Cardiovascular characteristics	
Current smoker	343 (78.0)
Quit-smoking > 1 year ago or never smoked	93 (21.1)
Diabetes	180 (40.9)
Insulin-dependent diabetes	62 (14.1)
Oral medication-controlled diabetes	89 (20.2)
Diet-controlled diabetes	28 (6.4)
Stroke or transient ischaemic attack	49 (11.1)
Ischaemic heart disease (previous event)	143 (32.5)
Hypertension	319 (72.5)
Hyperlipidaemia	
Total cholesterol > 4 mmol/l	192 (43.6)
Total cholesterol > 5 mmol/l	97 (22.0)
LDL cholesterol > 1.8 mmol/l	199 (45.2)
LDL cholesterol > 2.6 mmol/l	117 (26.6)
Cardiovascular medication	
Aspirin	124 (28.2)
Clopidogrel	84 (19.1)
Other antiplatelet	4 (0.9)
Dual antiplatelet therapy	12 (2.7)
≥ 1 antithrombotic agent	172 (39.1)
Anticoagulated	57 (13.0)
Angiotensin-converting enzyme inhibitor	183 (41.6)
Beta-blocker	112 (25.5)
Calcium channel blocker	144 (32.7)
Other antihypertensive agent	57 (13.0)
Antihyperlipidaemic medication	
Any statin	337 (76.6)
Atorvastatin	254 (57.7)
Simvastatin	55 (12.5)
Pravastatin	7 (1.6)

Other statin	21 (4.8)
High-dose statin therapy	49 (11.1)
Ezetimibe	21 (4.8)

*With percentages in parentheses unless indicated otherwise; *values are mean(s.d.). LDL, low-density lipoprotein.

Table 3 Lipid profiles and hyperlipidaemia prevalence depending on high-intensity statin prescribing			
	High-intensity statin therapy (*n* = 49)	**No high-intensity statin therapy (*n* = 391)**	***P*†**
Total cholesterol (mmol/l)*	4.3(1.6)	4.3(1.0)	0.724
≥ 4 mmol/l (% of patients)	49	43.0	0.422‡
LDL-cholesterol (mmol/l)*	2.4(1.4)	2.6(1.0)	0.798
≥ 1.8 mmol/l (% of patients)	51.0	44.5	0.589‡
HDL-cholesterol (mmol/l)*	1.1(0.5)	1.2(0.4)	0.331

*Values are mean(s.d.). LDL, low-density lipoprotein; HDL, high-density lipoprotein.
†Student's *t* test, except ‡χ_2 test.

Table 4 Benefits of optimal guideline-based medical therapy estimated using the SMART-REACH model

	Whole group (*n* = 352)	**High LDL-cholesterol (*n* = 272)**	**High BP (*n* = 241)**	**Smokers (*n* = 287)**	**No antithrombotic therapy (*n* = 181)**	**All risk factors (*n* = 351)**
Prognosis						
10-year CVD risk (%)	53 (44–62)	52 (43–59)	53 (44–64)	54 (45–62)	55 (47–65)	53 (44–62)
Lifetime CVD risk (%)	73 (68–78)	73 (67–78)	75 (71–79)	73 (69–78)	75 (71–79)	73 (68–78)
CVD-free life-expectancy (years)	74.6 (70.0–79.0)	74.5 (70.0–79.1)	74.9 (71.0–78.9)	74.0 (69.3–78.2)	74.4 (69.1–79.3)	74.6 (70.0–79.0)
Remaining CVD-free life-years	6.4 (4.8–8.5)	6.5 (5.1–8.7)	6.6 (4.9–8.7)	6.2 (4.7–8.1)	6.2 (4.6–8.0)	6.4 (4.8–8.5)
Treatment benefit						
10-year ARR (%)	5 (1–10)	7 (3–12)	20 (12–28)	14 (12–15)	7 (6–7)	29 (20–38)
Lifetime ARR (%)	4 (1–10)	6 (3–11)	19 (10–30)	8 (6–10)	5 (4–6)	29 (18–43)
Gain in CVD-free life expectancy (years)	0.6 (0.1–1.6)	1.0 (0.5–2.2)	3.3 (1.8–5.3)	2.9 (2.2–3.6)	0.9 (0.6–1.2)	6.3 (4.0–9.3)

Values are median (i.q.r.). LDL, low-density lipoprotein; CVD, cardiovascular disease; ARR, absolute risk reduction.

Typesetter: please use Fig. 1 for graphical abstract

Blurb Previous research has suggested that the medical management of patients with peripheral artery disease may be suboptimal. This national project assessed the medical therapy and lipid control of individuals with established peripheral artery disease and compared it against established guidelines/treatment targets. These individuals are currently not receiving appropriate care to address their cardiovascular risk factors, which has an impact on their predicted risk of future major cardiovascular morbidity. New pathways of treatment are required to address this important issue and improve outcomes.