Cardiovascular risk factors and the risk of major adverse limb events in patients with symptomatic cardiovascular disease

Steven HJ Hageman MD[1], Gert J de Borst MD, PhD[2], Jannick AN Dorresteijn MD, PhD[1], Michiel L Bots MD, PhD[3], Jan Westerink MD, PhD[1], Folkert W Asselbergs MD, PhD[4-6], Frank LJ Visseren, MD, PhD[1], on behalf of the UCC-SMART Study Group[7].

[1] Department of Vascular Medicine, University Medical Center Utrecht, Utrecht, The Netherlands

[2] Department of Vascular Surgery, University Medical Center Utrecht, Utrecht, The Netherlands

[3] Julius Center for Health Sciences and Primary Care, Utrecht, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

[4] Department of Cardiology, Division Heart & Lungs, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

[5] Institute of Cardiovascular Science, Faculty of Population Health Sciences, University College London, London, United Kingdom

[6] Health Data Research UK and Institute of Health Informatics, University College London, London, United Kingdom

[7] Members of the UCC-SMART-Study group are listed in the acknowledgement section.

Word count: 3000

Corresponding author

F.L.J. Visseren, MD, PhD

Department of Vascular Medicine, University Medical Centre Utrecht

PO Box 85500, 3508 GA Utrecht, The Netherlands

Phone: +31 (0)88 7555161; Fax: +31 (0)30 2523741

Email: F.L.J.Visseren@umcutrecht.nl

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in HEART editions and any other BMJPGL products to exploit all subsidiary rights

Abstract

Aims: To determine the relationship between non-high-density lipoprotein cholesterol (non-HDL-c), systolic blood pressure (SBP) and smoking and the risk of major adverse limb events (MALE) and the combination with major adverse cardiovascular events (MALE/MACE) in patients with symptomatic vascular disease.

Methods: Patients with symptomatic vascular disease were included from the Utrecht Cardiovascular Cohort - Secondary Manifestations of ARTerial disease (UCC-SMART) (1996–2017). The effects of non-HDL-c, SBP and smoking on the risk for MALE were analyzed with Cox proportional hazard models stratified for presence of peripheral artery disease (PAD). MALE was defined as major amputation, peripheral revascularization or thrombolysis in the lower limb.

Results: In 8139 patients (median follow-up 7.8 years, IQR 4.0-11.8) 577 MALE (8.7/1000 person-years) and 1933 MALE/MACE were observed (29.1/1000 person-years). In PAD patients there was no relation between non-HDL-c and MALE, in patients with coronary artery disease (CAD), cerebrovascular disease (CVD) or abdominal aortic aneurysm (AAA) the risk of MALE was higher per 1 mmol/L non-HDL-c (HR 1.14, 95%CI 1.01 -1.29). Per 10 mmHg SBP the risk of MALE was higher in PAD patients (HR 1.06, 95%CI 1.01-1.12) and CVD/CAD/AAA patients (HR 1.15, 95%CI 1.08-1.22). The risk of MALE was higher in smokers with PAD (HR 1.45, 95%CI 0.97-2.14) and CAD/CVD/AAA (HR 7.08, 95%CI 3.99-12.57).

Conclusions: The risk of MALE and MALE/MACE in patients with symptomatic vascular disease differs according to vascular disease location and is associated with non-HDL-c, SBP and smoking. These findings confirm the importance of MALE as an outcome and underline the importance of risk factor management in patients with vascular disease.

Word count abstract: 259

Keywords: Peripheral Arterial Disease, Vascular Disease, Amputation, Blood pressure, Smoking, Cholesterol

Key questions

What is already known about this subject?

Patients with symptomatic cardiovascular disease are not only at risk for recurrent major adverse cardiovascular events (MACE), but also for major adverse limb events (MALE). These events may lead to significant morbidity but are only rarely reported as a (primary) outcome in trials and cohorts. Classical risk factors for MACE may also increase the risk of MALE.

What does this study add?

The incidence of MALE and MALE/MACE in patients with symptomatic vascular disease differs according to vascular disease location, varying from 3.8/1000 person-years in patients with coronary artery disease (CAD) up to 29.9/1000 person-years in patients with peripheral artery disease (PAD). In patients with CAD, cerebrovascular disease or abdominal aortic aneurysm, the risk of MALE is higher in patients with higher non-high-density lipoprotein cholesterol (HR 1.14 per 1 mmol/L increase, 95%CI 1.01 -1.29), systolic blood pressure (HR 1.06 per 10 mmHg increase, 95%CI 1.01-1.12) and in smokers (HR 1.15, 95%CI 1.08-1.22). In order to guide preventive measures, the population attributable fractions were quantified for these modifiable risk factors, which show that a large fraction of incident MALE is attributable to systolic blood pressure and smoking.

How might this impact on clinical practice?

These findings confirm the importance of MALE as an outcome and underline the importance of classic risk factor management in patients with vascular disease, not only to prevent MACE, but also to prevent disabling MALE.

Introduction

Patients with symptomatic cardiovascular disease are at high risk for recurrent major adverse cardiovascular events (MACE). Major adverse limb events (MALE), including amputations and peripheral revascularizations, lead to significant morbidity[1–3] but are rarely reported as a (primary) outcome in trials and cohorts. Patients with peripheral artery disease (PAD) are at especially high risk of these events, having a 3-fold increase in incident MACE[4] and over 10-fold increase in MALE incidence.[5] Hypercholesterolemia is associated with a 20% higher risk of PAD in the general population[6] and 1 mmol/L reduction of low-density lipoprotein cholesterol (LDL-c) leads to a 22% decrease in MACE incidence.[7] Lipid lowering with a statin in PAD patients is associated with a 18% reduction of adverse limb outcomes.[8] The FOURIER trial showed that by lowering LDL-c with PCSK9-monoclonal antibody, the risk of MALE is lowered by 42% in comparison to placebo.[5] Non-high-density lipoprotein cholesterol (non-HDL-c) includes both LDL-c and remnant cholesterol and has a stronger association with cardiovascular outcomes in comparison to LDL-c.[9] Hypertension is associated with an increased risk of PAD and MALE in the general population.[10,11] In PAD patients however, it has been suggested that lowering blood pressure below a critical level may worsen PAD symptoms and progression by decreasing peripheral perfusion.[12] Smoking is one of the most important risk factors for PAD and is attributable to more than half of the prevalence of PAD.[13,14] Also, smoking cessation increases the amputation free survival in patients with PAD (Hazard ratio [HR] of 0.43, 95%CI 0.22-0.86).[15]

The aims of the current study were to determine the incidence of MALE and MALE/MACE in patients with symptomatic vascular disease, to assess to what extent non-HDL-c, SBP and smoking increase the risk of MALE and MALE/MACE and to quantify the population attributable fractions (PAF) of these risk factors.

Methods

Patients originate from the Utrecht Cardiovascular Cohort - Secondary Manifestations of ARTerial disease (UCC-SMART), a single-center ongoing prospective cohort study in Utrecht, the Netherlands. A detailed description of the study protocol has been described previously.[16] Study patients are newly referred patients to the University Medical Center Utrecht with atherosclerotic disease or increased risk for atherosclerotic disease and were included between January 1996 and March 2017 (supplementary figure 1). From this cohort, we included all patients with symptomatic PAD, coronary artery disease (CAD), cerebrovascular disease (CVD) and/or abdominal arterial aneurysm (AAA). PAD was defined as a symptomatic and documented obstruction of distal arteries of the leg (ankle brachial index ≤0.90), a revascularization procedure of the leg (percutaneous transluminal angioplasty or bypass surgery) or a prior amputation. CAD was defined as a clinical diagnosis of angina pectoris, myocardial infarction, cardiac arrest, or coronary revascularization, CVD as a clinical diagnosis of a transient ischemic attack or ischemic or hemorrhagic stroke and AAA was defined as a history of abdominal aortic surgery or an abdominal aortic anteroposterior diameter of ≥3 cm at baseline. The study was approved by the local Medical Ethics Committee and written informed consent was obtained from all patients. Patients and public were not involved in the design, conduct or reporting of this study.

Data collection

After inclusion, all baseline characteristics were determined using a standardized screening protocol consisting of questionnaires, physical examination, laboratory testing, ankle-brachial index (ABI), and abdominal aortic and carotid ultrasound. Non-HDL-c was defined as total cholesterol minus HDL-cholesterol and was measured from fasting venous blood samples, LDL-c was calculated using the Friedewald formula. Office SBP was measured in sitting position twice in the both arms, the highest mean of the measurements on one arm was used. Smoking and the amount of pack-years were self-reported. Diabetes mellitus (DM) at baseline was either self-reported DM type 1 or 2 or a fasting

glucose of >7.0 mmol/L at baseline. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Medication use was self-reported.

The primary outcome of this study was the incidence of MALE, a composite outcome consisting of a lower limb revascularization (vascular intervention or thrombolysis), and major amputation (at the level of the ankle or more proximal). Minor amputations were not regarded as a MALE in accordance to prior studies.[2,17] The incidence of MACE was assessed to serve as a comparison to MALE. MACE was a composite outcome consisting of non-fatal myocardial infarction, non-fatal stroke or vascular death. MALE/MACE was a composite outcome consisting of either MALE or MACE Patients received biannual questionnaires to evaluate possible endpoints. Whenever a possible event was reported, hospital discharge letters, GP letters, and results of relevant laboratory and radiology examinations were collected and the endpoint was verified by three independent experienced physicians from the UCC-SMART endpoint committee. Interventions already planned at inclusion in the UCC-SMART cohort were not regarded endpoints.

Data analyses

Because complete case analysis may lead to loss of statistical power and possible bias,[18] values of determinants or possible confounders were imputed by single regression imputation. Missing data was <1.0% except for C-reactive protein (CRP) (n=224, 2.8%). Follow-up was defined as time from inclusion until MALE-event, death, loss to follow-up (n=543, 6.7%) or until march 2017. Cox proportional hazards models were fitted to determine the effect of the risk factors on the risk of MALE, MACE or MALE/MACE. Presence of PAD at baseline was an effect modifier in the relation between the risk of MALE and non-HDL-c (p for interaction <0.01), SBP (p for interaction 0.01), and smoking (p for interaction <0.01). All models were stratified on presence of PAD at baseline. Using restricted cubic splines, there was no evidence for a non-linear relation between SBP and the incidence of MALE (p for nonlinearity 0.28), MACE (p for nonlinearity 0.06), and MALE/MACE (p for

nonlinearity 0.16). There was no evidence for violations of the proportional hazard assumption, assessed visually on plotted Schoenfeld residuals.

Potential confounders were selected prior to the analysis based on causal diagrams. To adjust for potential confounding factors the model investigating the relation between non-HDL-c and MALE and MACE occurrence was adjusted for age, sex, DM, SBP, smoking, statin use and eGFR. The presence of DM was no effect modifier for the relation between non-HDL-c and the occurrence of MALE (p for interaction 0.63). In the relation between SBP and the risk of MALE and MACE, the following possible confounders were added to the models: age, sex, non-HDL-c, smoking, DM, BMI and CRP. The relation between smoking and the risk MALE and MACE was adjusted for the possible confounders: age, sex, SBP, DM, BMI, non-HDL-c and eGFR. A dose-response relationship was assessed for the relation between smoking and the incidence of MALE and MACE for the categories 0-20 pack-years, 21-40 pack-years or >40 pack-years.

The PAF was quantified for all three relationships and was defined as the proportion of cases that could be prevented if the risk factor would be completely removed from the population. The PAF was based on Cox models adjusted for confounding factors using the R-package 'AF' (version 0.1.4).[19] In order to calculate the PAF, non-HDL-c was dichotomized at below or above 2.6 mmol/L, for SBP a cut-off at 140mmHg was used and smoking was analyzed as current smoking versus never or former smoking.

All analyses were performed with R-statistic programming (version 3.4.1, R Foundation for Statistical Computing, Vienna, Austria).

Sensitivity analyses

A sensitivity analysis was performed in which minor amputations were included in the definition of MALE. Because previous studies found a non-linear relation between SBP and the risk of MACE with a nadir around 140mmHg,[20,21] a separate analysis was done in which only people with a blood pressure of more than 140mmHg were included. Also, further exploratory Cox models were fitted for all relations in which atherosclerotic disease location, number of atherosclerotic disease locations,

HbA1C, aspirin, alcohol, eGFR, and different classes of antihypertensive drugs were added to the models. In order to assess the impact of competing risks, the analyses were repeated with Fine and Gray competing risk models.

Results

Baseline characteristics

A total of 8,139 patients were included with a total follow-up of 66,359 person-years (median follow up 7.8 years, IQR 4.0-11.8 years). The baseline characteristics of the included patients are presented in Table 1. The mean age was 60.0 ± 10.3 years, 74% percent of the patients were male, 61% had a history of CAD, 30% of CVD, 18% of PAD and 9% of AAA. Baseline characteristics across quartiles of non-HDL-c, SBP and smoking status are presented in supplementary Table 1-3.

Prescription frequencies of guideline medications increased over the years in the UCC-SMART cohort. In the first 10 years of inclusion (1996-2006), 54% of the patients was prescribed a statin and 24% an ACE-inhibitor, which increased to 80% statin use and 37% statin use after 2006. Patients with CAD were more often prescribed statins (82%) than patients with PAD (49%), CVD (58%) or AAA (51%).

Incidence rates of MALE and MACE

A total of 577 first MALE were observed, of which 48 were major amputations, 311 surgical interventions and 218 revascularizations (incidence rate 8.7/1000 person-years, Figure 1A). In patients with PAD at baseline 376 first MALE occurred (incidence rate 29.9/1000 person-years). In patients with a history of CAD but without PAD, the MALE incidence rate was 3.8 per 1000 person-years. For CVD, the MALE incidence rate was 4.1/1000 person-years and for AAA this incidence rate was 9.3/1000 person-years. The incidence rates were highest in patients with PAD + DM (44.6/1000 person-years) and PAD + polyvascular disease (36.1/1000 person-years).

A total of 1568 MACE were observed (incidence rate 24.0/1000 person-years, figure 1B). The incidence rate of MACE was 31.3/1000 in PAD patients. In the patients without PAD, the incidence rates were 21.8/1000 in CAD patients, 24.3/1000 in CVD patients and 47.4/1000 person-years in AAA patients. The combined endpoint MALE/MACE was observed 1933 times (incidence rate 29.1/1000 person-years, figure 1C), incidence rates per 1000 person-years were 57.3/1000 for PAD, 23.1/1000 for CAD, 25.4/1000 for CVD and 50.6/1000 for AAA.

Relation between non-HDL-c, SBP and smoking and occurrence of MALE, MACE and MALE/MACE

There was no significant relation between non-HDL-c and the occurrence of MALE, MACE or MALE/MACE in patients with PAD (Figure 2A). In patients with CAD/CVD/AAA but without PAD, the risk of all outcomes was higher with higher non-HDL-c.

There was a positive relation between SBP and the occurrence of MALE, MACE and MALE/MACE in patients with PAD (Figure 2B). In patients with CAD/CVD/AAA but without PAD, the occurrence of MALE and MALE/MACE was positively related to SBP, there was no significant effect of SBP on MACE.

In patients with PAD, former and current smoking increased the risk of MALE insignificantly (figure 3). In these patients, both former and current smoking were associated with an increased risk of MACE and MALE/MACE. In patients with CAD/CVD/AAA but without PAD, former and current smoking increased the risk of MALE, MACE and MALE/MACE.

A dose response effect was observed in the relation between smoking and MALE. In comparison to smokers with <20 pack-years, the risk was increased for 21-40 pack-years (HR 1.45, 95%CI 1.18-1.78) and >40 pack-years (HR 2.18, 95%CI 1.54-2.38). A similar effect was observed for MACE (HR 1.10, 95%CI 9.97-1.10 for 21-40 pack-years and HR 1.25, 95%CI 1.09-1.45 for >40 pack-years) and MALE/MACE (HR 1.19, 95%CI 1.07-1.34 for 21-40 pack-years and HR 1.41, 95%CI 1.25-1.61 for >40 pack-years).

Population attributable fraction

The PAF of incident MALE in PAD patients was 5% (95%CI 0-31) for non-HDL-c, 9% (95%CI 0-19) for SBP and 7% (95%CI 0–16) for smoking. In patients with CAD/CVD/AAA this was 0% (95%CI 0-27) for non-HDL-c, 18% (95%CI 5-31) for SBP and 28% (95%CI 18-36) for smoking (figure 4).

Sensitivity analyses

Including minor amputations in the MALE endpoint resulted in 15 additional MALE events, repeating the analyses with this definition of MALE did not meaningfully change the relations between risk factors and risk of MALE. The effect of non-HDL-c, SBP and smoking on the risk of MALE was similar in the highest risk groups, PAD + DM or PAD + polyvascular disease (supplementary table 4), except for current smoking in patients with PAD + DM. In this group current smoking led to a non-significant lower risk of MALE. Inclusion of only patients with a SBP of $\geq$140 mmHg SBP led to a stronger relation between SBP and risk of MACE in the patients with PAD (HR 1.16, 95%CI 1.07-1.25) but did no change the estimate in patients with CAD/CVD/AAA. There was no effect on the risk of MALE in both groups. Further adjustment for additional possible confounders did not change the estimates meaningfully. The competing-risk adjusted analysis showed similar results as the main analysis (supplementary table 5).

Discussion

In the present study it is shown that the incidence of MALE and MALE/MACE differs according to vascular disease location. The highest incidence of MALE was observed in patients with PAD, in these patients the incidence of MALE was higher than of MACE. In patients with CAD/CVD/AAA, higher non-HDL-c, higher SBP and smoking were associated with an increased risk of MALE, the effect of smoking and SBP on the incidence of MALE was much stronger than on the incidence of MACE.

In previously published studies it is shown that lipid-lowering therapy resulted in a reduction in amputations or limb events in patients with PAD.[8,22,23] In the FOURIER trial, a 42% reduction in MALE incidence was shown after treatment with a PCSK9-inhibitor in comparison to placebo.[5] In contrast to the current study, non-urgent revascularizations were not included in the MALE-endpoint of the FOURIER trial. In FOURIER's secondary endpoint consisting of all peripheral revascularizations, no difference was observed, indicating non-HDL-c may not be associated with non-urgent revascularizations. Therefore, inclusion of non-urgent revascularizations in the current study may have weakened the observed relation between non-HDL-c and the incidence of MALE.

The positive relation between SBP and risk of MALE as observed in this study is consistent with earlier studies in patients in the general population or with PAD.[10,11,24,25] Results from the current study show that SBP also increases the risk of MALE in patients with vascular disease at other locations and that this effect is stronger than on the incidence of MACE. These estimates did not change when only patients with a SBP of $\geq$140 mmHg were analyzed to account for a potential J-shaped relationship.

Current smoking is a strong risk factor for incident MALE and PAD, which is consistent with previously published results.[15,26] Results from the current study show that this effect is very strong in patients with CAD/CVD/AAA and that the effect of smoking on the incidence of MALE is stronger than on the incidence of MACE. Previous studies reported a dose-dependent relation between smoking and the incidence and prevalence of PAD,[13,26,27] results from the current study show that a similar effect also applies to incident MALE.

The effects of non-HDL-c, SBP and smoking on the incidence of MALE were smaller in patients with PAD in comparison to in patients with CAD/CVD/AAA. These differences could be partially explained by a difference in pathophysiology. In patients without PAD, MALE may primarily be a result generalized progression of atherosclerosis, whereas a recurrent MALE might also occur due to restenosis or thrombosis of a peripheral artery stent or bypass in patients with PAD. However, it is also possible that these differences are due to selection on the index event. This can be understood by viewing the onset of PAD as the sum of the effect of multiple causal factors. If one very strong causal factor, for example smoking, is already present, less effect of the other factors is required for the onset of disease. Subsequently comparing the smokers and non-smokers that have already developed PAD

leads to the smokers having a relatively healthy risk profile in comparison to the non-smokers in both measured and non-measured factors, which cannot be completely corrected for.[28]

Because the FOURIER study found similar relative effect sizes on the incidence of MALE in patients with PAD as in patients with vascular disease at other locations from lipid-lowering,[5] it is likely that the actual effect is closer towards the estimate of the CAD/CVD/AAA group.

Results from the current study contribute to the evidence that the modifiable risk factors for MACE also increase the risk of MALE in patients with symptomatic vascular disease, including patients with preexisting PAD. In comparison to MACE, the fraction of MALE that can be attributed to the modifiable risk factors SBP and smoking is even larger. This implies that improved risk factor management in patients with symptomatic atherosclerotic disease could prevent many cases of incident MALE, apart from the benefit on reduction of MACE risk. In light of the high incidence the numbers needed to treat are expected to be low. The morbidity associated with MALE can be very high and a large fraction is attributable due to treatable risk factors, inclusion of those events in (primary) composite outcomes of intervention studies as MALE/MACE could therefore better reflect the effect of an intervention on the total disease burden due to atherosclerotic disease.

Strengths of this prospective cohort study include the large number of patients with symptomatic atherosclerotic disease with long and complete follow-up, resulting in a high number of MALE and MACE. Also, the generalizability of the results is high as the UCC-SMART cohort resembles a referred patient population with vascular disease. A possible limitation is the fact that baseline characteristics were only recorded at the start of the study but may have changed in the duration of the follow-up. Furthermore, the results in patients with PAD may have been affected by selection on the index event and are therefore expected to be closer to the results in the CAD/CVD/AAA group.

In conclusion, the incidence of MALE in patients with clinical manifest vascular disease differs according to vascular disease location and is associated with non-HDL-c, SBP and smoking. A large fraction of incident MALE is attributable to modifiable risk factors. These findings confirm the importance of MALE as an outcome and underline the importance of classic risk factor management in patients with vascular disease, not only to prevent MACE, but also to prevent disabling MALE.

Acknowledgements

We gratefully acknowledge the contribution of the research nurses; R. van Petersen (data-manager); B. van Dinther (study manager) and the members of the Utrecht Cardiovascular Cohort-Second Manifestations of ARTerial disease-Studygroup (UCC-SMART-Studygroup): F.W. Asselbergs and H.M. Nathoe, Department of Cardiology; G.J. de Borst, Department of Vascular Surgery; M.L. Bots and M.I. Geerlings, Julius Center for health Sciences and Primary Care; M.H. Emmelot, Department of Geriatrics; P.A. de Jong and T. Leiner, Department of Radiology; A.T. Lely, Department of Obstetrics & Gynecology; N.P. van der Kaaij, Department of Cardiothoracic Surgery; L.J. Kappelle and Y.M. Ruigrok, Department of Neurology; M.C. Verhaar, Department of Nephrology, F.L.J. Visseren (chair) and J. Westerink, Department of Vascular Medicine, University Medical Center Utrecht and Utrecht University.

Funding

The UCC- SMART study was financially supported by a grant of the University Medical Center Utrecht. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of interest

Folkert Asselbergs is supported by UCL Hospitals NIHR Biomedical Research Centre. The other authors report no conflicts of interest

Author contributions

GB, MB, JW, FA and FV contributed to the design and conduct of the data acquisition. Design of the paper and analysis was done by SH, JD and FV. All authors contributed to the interpretation of the results. All authors have reviewed and approved the final manuscript.

References

1. Mahoney EM, Wang K, Keo HH, et al. Vascular hospitalization rates and costs in patients with peripheral artery disease in the United States. *Circ Cardiovasc Qual Outcomes* 2010; 3: 642–651.
2. Anand SS, Caron F, Eikelboom JW, et al. Major Adverse Limb Events and Mortality in Patients With Peripheral Artery Disease. *J Am Coll Cardiol* 2018; 71: 2306–2315.
3. Duval S, Keo HH, Oldenburg NC, et al. The impact of prolonged lower limb ischemia on amputation, mortality, and functional status: The FRIENDS registry. *Am Heart J* 2014; 168: 577–587.
4. Aboyans V, Desormais I, Lacroix P, et al. The General Prognosis of Patients With Peripheral Arterial Disease Differs According to the Disease Localization. *J Am Coll Cardiol* 2010; 55: 898–903.
5. Bonaca MP, Nault P, Giugliano RP, et al. Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease. *Circulation* 2018; 137: 338–350.
6. Fowkes FGR, Rudan D, Rudan I, 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.
7. Baigent C, Blackwell L, Emberson J, 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.
8. Kumbhani DJ, Steg PG, Cannon CP, et al. Statin therapy and long-term adverse limb outcomes in patients with peripheral artery disease: insights from the REACH registry. *Eur Heart J* 2014; 35: 2864–2872.
9. Boekholdt SM, Arsenault BJ, Mora S, et al. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients

treated with statins: a meta-analysis. *JAMA* 2012; 307: 1302–9.

10. Emdin CA, Anderson SG, Callender T, et al. Usual blood pressure, peripheral arterial disease, and vascular risk: cohort study of 4.2 million adults. *BMJ* 2015; 351: h4865.

11. Itoga NK, Tawfik DS, Lee CK, et al. Association of Blood Pressure Measurements With Peripheral Artery Disease Events. *Circulation* 2018; 138: 1805–1814.

12. Lane DA, Lip GY. Treatment of hypertension in peripheral arterial disease. *Cochrane Database Syst Rev* 2013; 10–13.

13. Willigendael EM, Teijink JAW, Bartelink M, et al. Influence of smoking on incidence and prevalence of peripheral arterial disease. *J Vasc Surg* 2004; 40: 1158–1165.

14. Lu JT, Creager MA. The relationship of cigarette smoking to peripheral arterial disease. *Rev Cardiovasc Med* 2004; 5: 189–93.

15. Armstrong EJ, Wu J, Singh GD, et al. Smoking cessation is associated with decreased mortality and improved amputation-free survival among patients with symptomatic peripheral artery disease. *J Vasc Surg* 2014; 60: 1565–1571.

16. Simons PCG, Algra A, Van De Laak MF, et al. Second manifestations of ARTerial disease (SMART) study: Rationale and design. *Eur J Epidemiol* 1999; 15: 773–781.

17. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med* 2017; 376: 1713–1722.

18. Donders ART, van der Heijden GJMG, Stijnen T, et al. Review: A gentle introduction to imputation of missing values. *J Clin Epidemiol* 2006; 59: 1087–1091.

19. Sjölander A, Vansteelandt S. Doubly robust estimation of attributable fractions in survival analysis. *Stat Methods Med Res* 2017; 26: 948–969.

20. Dorresteijn JAN, van der Graaf Y, Spiering W, et al. Relation Between Blood Pressure and Vascular Events and Mortality in Patients With Manifest Vascular Disease. *Hypertension* 2012; 59: 14–21.

21. Bangalore S, Messerli FH, Wun C-C, et al. J-curve revisited: an analysis of blood pressure and cardiovascular events in the Treating to New Targets (TNT) Trial. *Eur Heart J* 2010; 31: 2897–2908.

22. Arya S, Khakharia A, Binney ZO, et al. Association of Statin Dose With Amputation and Survival in Patients With Peripheral Artery Disease. *Circulation* 2018; 137: 1435–1446.
23. 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: 645–655.
24. Joosten MM, Pai JK, Bertoia ML, et al. Associations Between Conventional Cardiovascular Risk Factors and Risk of Peripheral Artery Disease in Men. *JAMA* 2012; 308: 1660.
25. Rapsomaniki E, Timmis A, George J, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. *Lancet* 2014; 383: 1899–1911.
26. Conen D, Everett BM, Kurth T, et al. Smoking, smoking cessation and risk for symptomatic peripheral artery disease in women: a cohort study. *Ann Intern Med* 2011; 154: 719–26.
27. Lee Y-H, Shin M-H, Kweon S-S, et al. Cumulative smoking exposure, duration of smoking cessation, and peripheral arterial disease in middle-aged and older Korean men. *BMC Public Health* 2011; 11: 94.
28. Dahabreh IJ, Kent DM. Index Event Bias as an Explanation for the Paradoxes of Recurrence Risk Research. *JAMA* 2011; 305: 822.

Table 1: Patient characteristics according to vascular disease location

	PAD	**Patients without PAD (n = 6,684)**		
		CAD	**CVD**	**AAA**
	n = 1,455	n = 4,537	n = 2,266	n = 571
Male sex	983 (68%)	3,695 (81%)	1,410 (62%)	489 (86%)
Age (years)	59.6 ± 10.5	60.7 ± 9.6	59.0 ± 11.3	65.0 ± 9.5
Former smoker	558 (38%)	2,388 (53%)	992 (44%)	308 (54%)
Current smoker	755 (52%)	1,062 (23%)	714 (32%)	186 (33%)
Packyears (years)	27.2 ± 19.8	18.4 ± 19.3	18.6 ± 20.0	26.7 ± 22.5
Body mass index (kg/m²)	26.3 ± 4.2	27.3 ± 3.8	26.6 ± 4.3	26.5 ± 3.9
Diastolic blood pressure (mmHg)	81 ± 12	80 ± 11	82 ± 12	84 ± 12
Systolic blood pressure (mmHg)	145 ± 21	137 ± 20	141 ± 22	143 ± 20
Ankle brachial index	0.9 ± 0.2	1.2 ± 0.1	1.1 ± 0.2	1.1 ± 0.2
Diabetes mellitus	296 (20%)	848 (19%)	345 (15%)	79 (14%)
Coronary artery disease	402 (28%)	4,537 (100%)	401 (18%)	238 (42%)
Peripheral artery disease	1,455 (100%)	0 (0%)	0 (0%)	0 (0%)
Cerebrovascular disease	196 (13%)	401 (9%)	2,266 (100%)	87 (15%)
Abdominal aortic aneurysm	122 (8%)	238 (5%)	87 (4%)	571 (100%)
No. of vascular disease locations				
1	867 (60%)	3,934 (87%)	1,814 (80%)	282 (49%)
2	463 (32%)	567 (12%)	416 (18%)	253 (44%)
3	125 (9%)	36 (1%)	36 (2%)	36 (6%)
Laboratory values				
Total cholesterol (mmol/l)	5.3 ± 1.2	4.6 ± 1.1	4.9 ± 1.2	5.1 ± 1.3
LDL-cholesterol (mmol/l)	3.2 ± 1.1	2.6 ± 0.9	2.9 ± 1.1	3.1 ± 1.1
HDL-cholesterol (mmol/l)	1.2 ± 0.4	1.2 ± 0.3	1.3 ± 0.4	1.2 ± 0.4
Non-HDL cholesterol (mmol/l)	4.1 ± 1.3	3.4 ± 1.1	3.6 ± 1.2	3.9 ± 1.3
Triglycerides (mmol/l)	1.9 ± 1.4	1.7 ± 1.4	1.6 ± 1.2	1.7 ± 1.1
Estimated GFR (ml/min/1.73m²)	76 ± 20	77 ± 17	77 ± 18	70 ± 20
Medication use				
Statin	708 (49%)	3,695 (81%)	1,325 (58%)	290 (51%)
Diuretics	277 (19%)	968 (21%)	527 (23%)	158 (28%)
ACE inhibitors	347 (24%)	1,694 (37%)	638 (28%)	168 (29%)
Beta-blockers	421 (29%)	3,407 (75%)	694 (31%)	232 (41%)
Calcium channel blockers	287 (20%)	1,127 (25%)	358 (16%)	132 (23%)
Platelet inhibitor	797 (55%)	3,815 (84%)	1,525 (67%)	306 (54%)
Oral anticoagulants	202 (14%)	550 (12%)	213 (9%)	74 (13%)

PAD, peripheral artery disease; CAD, coronary artery disease; CVD, cerebrovascular disease; AAA, abdominal aortic aneurysm; HDL, high-density lipoprotein cholesterol; GFR, glomerular filtration rate (calculated with Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula). All data in n (%) or mean ± standard deviation

Figure 1: MALE-free, MACE-free and MALE/MACE-free survival according to vascular disease location at baseline

Kaplan-Meier curves according to atherosclerotic disease location. Patients in CAD, CVD and AAA groups do not have PAD at baseline. MALE, Major Adverse Limb Events; MACE, Major Adverse Cardiovascular Events; PAD, peripheral artery disease; CAD, coronary artery disease; CVD, cerebrovascular disease; AAA, abdominal aortic aneurysm.

Figure 2: Relation between non-HDL-c and SBP and the risk of MALE, MACE and MALE/MACE according to vascular disease location

This figure shows the hazard rates for the risk of MALE, MACE and MALE/MACE per mmol increase of non-HDL-c (A) and per 10mmHg increase of SBP (B). A was adjusted for: age, sex, SBP, DM, smoking and eGFR, B for age, sex, non-HDL-c, smoking, DM, BMI and CRP. PAD, peripheral artery disease; CAD, coronary artery disease; CVD, cerebrovascular disease; AAA, abdominal aortic aneurysm; MALE Major Adverse Limb Events; MACE, Major Adverse Cardiovascular Events.

Figure 3: Relation between smoking and the risk of MALE, MACE and MALE/MACE according to vascular disease location

The figure shows the hazard ratios of current smoking versus never smoking for MALE, MACE and MALE/MACE. Hazard ratios for former smoking are displayed in supplementary figure 1.Models were adjusted for: age, sex, SBP, non-HDL-c, DM, BMI and eGFR. PAD, peripheral artery disease; CAD, coronary artery disease; CVD, cerebrovascular disease; AAA, abdominal aortic aneurysm; MALE. Major Adverse Limb Events; MACE, Major Adverse Cardiovascular Events.

Figure 4: The population attributable fractions of MALE and MACE for elevated non-HDL-c, elevated SBP and smoking

This figure shows the population attributable fractions of incident MALE and MACE attributable to non-HDL-c (>2.6 mmol/L), SBP (>140mmHg) and current smoking ±95% confidence intervals for patients with (A) PAD and (B) CAD/CVD/AAA. The PAF is the proportion of cases that could be prevented if the risk factor would be completely removed from the population. PAD, peripheral artery disease; CAD, coronary artery disease; CVD, cerebrovascular disease; AAA, abdominal aortic aneurysm; MALE, Major Adverse Limb Events; MACE, Major Adverse Cardiovascular Events; non-HDL-C, non-high-density lipoprotein cholesterol; SBP, systolic blood pressure.