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ZDRUŽENJE ZA ŽILNE BOLEZNI

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Review

Lipid-lowering and anti-thrombotic therapy in patients with peripheral arterial disease

European Atherosclerosis Society/European Society of Vascular Medicine Joint Statement

Jill J. F. Belch[1], Marianne Brodmann[2], Iris Baumgartner[3], Christoph J. Binder[4], Manuela Casula[5,6], Christian Heiss[7,8], Thomas Kahan[9], Paolo Parini[10], Pavel Poredos[11], Alberico L. Catapano[6,12,*], and Lale Tokgözoğlu[13,*]

[1] The Institute of Cardiovascular Research, University of Dundee, Ninewells Hospital and Medical School, Ninewells Hospital, Dundee, UK
[2] Division of Angiology, Medical University, Graz, Austria
[3] Swiss Cardiovascular Centre, Division of Angiology, Bern University Hospital, University of Bern, Switzerland
[4] Department of Laboratory Medicine, Medical University of Vienna, Austria
[5] Epidemiology and Preventive Pharmacology Service (SEFAP), Department of Pharmacological and Biomolecular Sciences, University of Milan, Italy
[6] IRCCS MultiMedica, Milan, Italy
[7] Department of Clinical and Experimental Medicine, University of Surrey, Guildford, UK
[8] Surrey and Sussex Healthcare NHS Trust, East Surrey Hospital, Redhill, UK
[9] Division of Cardiovascular Medicine, Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden
[10] Department of Medicine and Department of Laboratory Medicine, Karolinska Institutet, and Theme Inflammation and Ageing, Karolinska University Hospital, Stockholm, Sweden
[11] Department of Vascular Disease, University Medical Centre Ljubljana, Slovenia
[12] Department of Pharmacological and Biomolecular Sciences, Università degli Studi di Milano, Italy
[13] Department of Cardiology, Hacettepe University Faculty of Medicine, Ankara, Turkey
* The authors are both senior authors

Summary: Patients with peripheral arterial disease (PAD) are at very high risk of cardiovascular events, but risk factor management is usually suboptimal. This Joint Task Force from the European Atherosclerosis Society and the European Society of Vascular Medicine has updated evidence on the management on dyslipidaemia and thrombotic factors in patients with PAD. Guidelines recommend a low-density lipoprotein cholesterol (LDLC) goal of more than 50% reduction from baseline and <1.4 mmol/L (<55 mg/dL) in PAD patients. As demonstrated by randomized controlled trials, lowering LDL-C not only reduces cardiovascular events but also major adverse limb events (MALE), including amputations, of the order of 25%. Addition of ezetimibe or a PCSK9 inhibitor further decreases the risk of cardiovascular events, and PCSK9 inhibition has also been associated with reduction in the risk of MALE by up to 40%. Furthermore, statin- based treatment improved walking performance, including maximum walking distance, and pain-free walking distance and duration. This Task Force recommends strategies for managing statin-associated muscle symptoms to ensure that PAD patients benefit from lipid-lowering therapy. Antiplatelet therapy, either daily clopidogrel 75 mg or the combination of aspirin 100 mg and rivaroxaban (2×2.5 mg) is also indicated to prevent cardiovascular events. Dual pathway inhibition (aspirin and rivaroxaban) may be considered following revascularization, taking into account bleeding risk. This Joint Task Force believes that adherence with these recommendations for lipid-lowering and antithrombotic therapy will improve the morbidity and mortality in patients with PAD.

Keywords: Peripheral arterial disease, lipid lowering, treatment targets

Introduction

Peripheral arterial disease (PAD), characterised by atherosclerosis in the arteries of the lower limb, poses an increasing health and societal burden world-wide. Already affecting more than 20% of individuals aged over 60 years [1 2], the prevalence will escalate as the population ages. This is highly relevant given that cardiovascular risk is higher among PAD patients than those with coronary artery disease (CAD) alone and increases with disease severity (Figure 1) [3, 4, 5]. Five-year mortality with PAD is almost double that of CAD (25% versus 13%) and higher than for many cancers, equating almost exactly to Duke's stage B carcinoma of colon [3, 6, 7]. Despite recognition of this high attrition rate, however, mortality associated with PAD has essentially remained unchanged over the past 25 years (Figure 2) [3, 8], unlike the decline evident for CAD [3, 9, 10]. This poor prognosis can be largely attributed to sub-optimal management of cardiovascular risk factors [9], as recommended by evidence-based guidelines [11, 12, 13].

Although PAD and CAD are both caused by atherosclerosis and share common lesion features, the clinical course, therapeutic response and certain demographic features suggest that there are factors that make PAD subjects more susceptible to the clinical manifestations of atherosclerosis [14]. PAD is characterised by higher levels of systemic inflammation markers, and a higher prevalence of diabetes than CAD [15]. As for all phenotypes of atherosclerosis, dyslipidaemia is one of the most important modifiable cardiovascular risk factors in PAD [16].

The European Society of Vascular Medicine (ESVM) and the European Atherosclerosis Society (EAS) recognise the need for a renewed focus on the management of PAD. This Joint Statement provides clear and updated evidence-based consensus on the management on dyslipidaemia and thrombotic factors, with the aim of decreasing the appalling cardiovascular morbidity and mortality associated with PAD.

Lipid-lowering therapies in PAD

What is the evidence that elevated lipids and lipoproteins increase risk for PAD?

Despite controversy over the years, elevated lipids are now known to be associated with increased cardiovascular risk in PAD [16]. Indeed, in a previous report, a discordant lipid profile was reported in patients with PAD compared to unaffected controls [17]. As with all phenotypes of atherosclerosis, apolipoprotein (apo)B-containing lipoproteins, which include all lipoproteins except high-density lipoproteins (HDL), are key players driving the initiation and progression of disease [18]. The archetypal apoB-containing lipoprotein is low-density lipoprotein (LDL), which is established as causal for atherosclerotic cardiovascular disease (ASCVD) [19, 20]. There is also accumulating evidence to suggest a causal role for triglyceride-rich lipoproteins and their remnant particles in atherosclerosis [21].

ApoB-containing lipoproteins retained in the arterial wall initiate the atherosclerotic process [18]. Higher levels of apoB-containing lipoproteins in plasma promote the development and progression of atherosclerotic plaques. Hence, the concentration and total duration exposure of apoB-containing lipoproteins, together with the concentration of circulating LDL cholesterol (LDL-C), represent the overall atherosclerotic plaque burden of an individual person [22, 23].

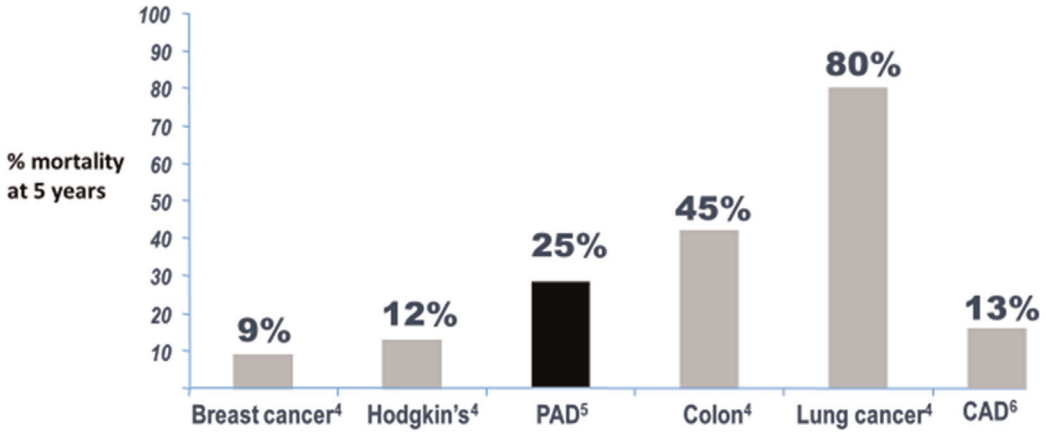
An increased ratio of apoB/apoAI (the apolipoprotein in HDL) was predictive of PAD risk in middle aged healthy men [24]. Genetic and epidemiologic studies provide insights into the role of specific apoB-containing lipoproteins that determine this risk. A genome-wide association study including over 30,000 PAD patients and 210,000 controls of the Million Veteran Program (MVP) identified variants in the genes encoding the LDL receptor (*LDLR*), lipoprotein lipase (*LPL*), and lipoprotein(a) [Lp(a)] (*LPA*) as drivers of PAD [25]. Interestingly, in replication analyses in more than 5,000 PAD patients from the UK Biobank, the *LPA* variant was the top locus associated with PAD. This finding is supported by an epidemiologic study showing a dose-dependent association of Lp(a) molar concentration and PAD [26].

The MVP study also identified several variants that were associated with either hypercholesterolaemia or hypertriglyceridaemia and PAD [25]. These findings are important as epidemiologic support for an association between elevated LDL-C concentration and PAD is less consistent than for CAD. For example, in the Health Professionals Follow-up Study, hypercholesterolaemia contributed 17% of the PAD risk [27]. Furthermore, associations of total cholesterol levels, total cholesterol/HDL ratio, and triglyceride concentration with PAD were often attenuated or abrogated after multivariate adjustment [28]. More recently, a prospective study of more than 27,000 women without incident PAD found that elevated LDL-particle number (based on nuclear magnetic resonance measurement) and triglyceride-rich lipoproteins but not LDL-C concentration were associated with PAD risk [29].

While some uncertainties persist regarding the contribution of individual apoB-containing lipoproteins to the different clinical manifestations of atherosclerosis, particularly in symptomatic PAD, overwhelming evidence supports the collective role of these lipoproteins in driving PAD. Moreover, as LDL-C is unequivocally established as causal for ASCVD [19], it is therefore the primary target when treating dyslipidaemia in patients with PAD [30].

What are the lipid goals in PAD?

The 2019 European Society of Cardiology/EAS dyslipidaemia guidelines recommend LDL-C goals according to the 10-year risk for fatal cardiovascular events. Patients with PAD belong in the very high-risk category, with



[4]American Cancer Society. Cancer Facts and Figures – https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf. [5]Sartipy et al. Eur J Vasc Endovasc Surg. 2018 Apr;55(4):529-536. doi: 10.1016/j.ejvs.2018.01.019. [6] Droz-Perroteau C. Six-year survival study after myocardial infarction: The EOLE prospective cohort study. Long-term survival after MI. https://doi.org/10.1016/j.therap.2019.02.001

Figure 1. Comparison of 5-year mortality rates: PAD versus common cancers.

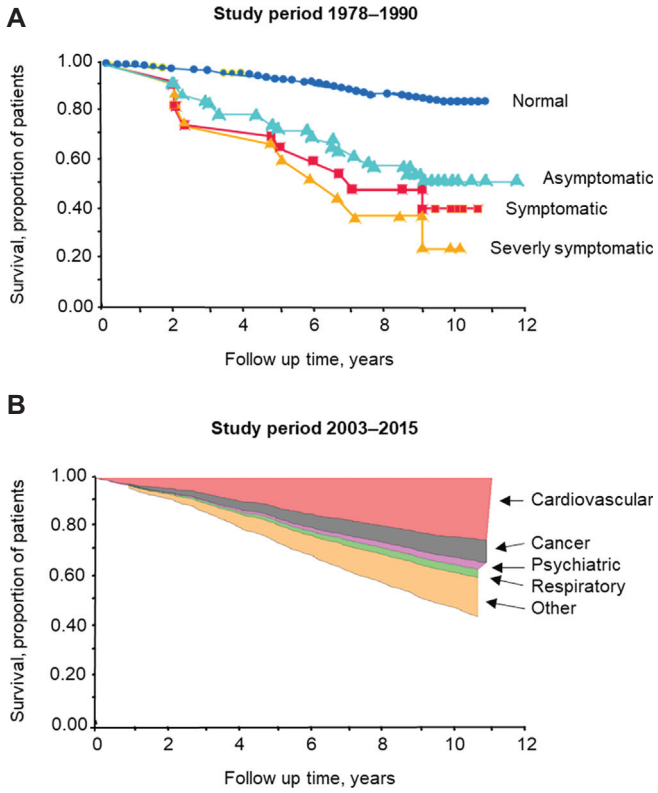


Figure 2. Little change in PAD patient survival over the last 25 years. Comparison of 10-year survival (A) between 1978 and 1990 (modified from Criqui et al. [10]) and (B) between 2003 and 2015 (according to cause of death) (modified from Sartipy et al. [3]).

≥10% risk of a fatal cardiovascular event. In these patients, both LDL-C reduction by ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended [30].

To attain this LDL-C goal treatment with a high-intensity statin at the maximal tolerated dose is recommended. If patients are unable to attain goal or report statin intolerance, a combination of statin (at a lower dose if statin intolerant) with ezetimibe is recommended, with addition of a PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor if further LDL-C lowering is indicated [31]. Lipid levels should be monitored 8 (±4) weeks after starting or adjusting treatment until LDL-C goal is achieved, and thereafter at least annually or as indicated.

Despite guideline recommendations, however, PAD patients are often underdiagnosed and inadequately managed compared with CAD patients, both for lifestyle intervention and pharmacotherapy [32]. As with other very

Table I. Effect of statin treatment on cardiovascular and major adverse limb events in patients with peripheral arterial disease

Outcome	Relative risk reduction (%)	Hazard ratio (95% CI)
Composite cardiovascular events	34	0.662 (0.59–0.741)
Cardiovascular death	41	0.594 (0.455–0.777)
All-cause death	39	0.608 (0.543–0.680)
Major adverse limb events	30	0.702 (0.605–0.815)
Amputation	35	0.654 (0.522–0.819)

Results from a meta-analysis of 51 studies in 138,060 patients, 35% treated with a statin. Derived from Pastori et al. [39].

high-risk groups, registries show disappointing results in terms of adherence with lifestyle and LDL-C goal achievement. In a study of symptomatic PAD patients, less than three-quarters did not attain an LDL-C level below 1.8 mmol/L (70 mg/dL) and nearly half had LDL-C levels above 2.5 mmol/L (100 mg/dL) [33]. Similar findings were reported among PAD patients included in studies of high cardiovascular risk populations [34, 35].

What is the evidence that lipid-lowering therapy improves outcome in PAD?

While lipid-lowering therapy indisputably reduces cardiovascular events in patients with CAD, evidence from prospective well-powered studies in PAD patients is more limited. In a systematic review of 18 trials of different lipid-lowering agents in 10,000 patients with lower limb PAD, lowering LDL-C concentration was associated with 20% reduction in total cardiovascular events and improvements in total walking distance and pain-free walking distance, but not ankle brachial index (ABI) [36]. Evidence for individual lipid-lowering therapies is summarized below.

Statins

Statins are guideline-recommended first line lipid-lowering therapy in patients with PAD, supported by definitive evidence of cardiovascular morbidity and mortality benefits [12, 37, 38]. Furthermore, there is also support for positive effects of lipid-lowering on major adverse limb events (MALE), as well as walking performance in patients with PAD.

Major adverse cardiovascular events (MACE) and MALE

There is clear evidence that statin treatment substantially improves cardiovascular outcomes and MALE in PAD patients. One meta-analysis evaluated 51 studies (2 randomized controlled trials, 20 prospective studies, and 29 retrospective studies) in 138,060 PAD patients with either stable claudication, critical limb ischaemia (CLI) or undergoing lower extremity revascularization, of whom 35% received a statin [39]. MACE included all-cause death, composite cardiovascular endpoints, cardiovascular death and stroke, and MALE included amputation and graft occlusion/revascularization. Statin treatment not only reduced all-cause mortality by 39%, cardiovascular death by 41%, cardiovascular outcomes by 34% and ischaemic stroke by 28%, but also reduced MALE by 30% and amputations by 35% (Table I). Another meta-analysis of 19 studies in 26,985 patients with CLI, about half on a statin, showed 25% reduction in amputation and 38% reduction in fatal events. Statin therapy was also associated with improved overall patency rates and lower incidence of MACE [40].

To some extent findings from these meta-analyses are confounded by inclusion of retrospective studies, as well as the fact that generally less than half of these patients were on a statin. To address these issues, this Joint Task Force conducted a meta-analysis of randomized controlled trials of statin-based treatment identified by MEDLINE searches which reported major cardiovascular events, cardiovascular mortality, or all-cause mortality in PAD patients [41, 42, 43, 44, 45]. Estimates for between group differences (statin vs. control) were derived using both fixed-effects (Mantel & Haenszel method) [46] and random-effects models (DerSimonian & Laird method) [47], with the latter reported if there was significant heterogeneity. Overall, this analysis showed that statin treatment reduced MACE by 24% (odds ratio 0.76, 95% confidence interval [CI] 0.69–0.83), cardiovascular death by 17% (odds ratio 0.83, 95% CI: 0.26–2.60) and all-cause mortality by 18% (odds ratio 0.82, 95% CI: 0.69–0.97) (Figure 3).

Outcome after limb intervention

There are limited data for the effect of statin treatment on outcomes after surgical and endovascular procedures. Pooled analysis of seven studies in patients with CLI, did, however, indicate that statin treatment was associated with lower rates of loss of patency (hazard ratio: 0.80, 95% CI: 0.66–0.96) [40].

Claudication development

There is some evidence that statin treatment can decrease the development and progression of PAD. For example, analyses from the Scandinavian Simvastatin Survival Study (4S), showed that cholesterol lowering with simvastatin reduced the incidence of carotid bruits and cerebrovascular events, as well as new-onset or worsening of angina pectoris and intermittent claudication [48]. The authors concluded that simvastatin may have a general anti-atherosclerotic effect not limited to the coronary bed. More recently, investigation of atheroma burden using serial whole body magnetic resonance angiography over 3 years showed that individuals with atheroma progression at

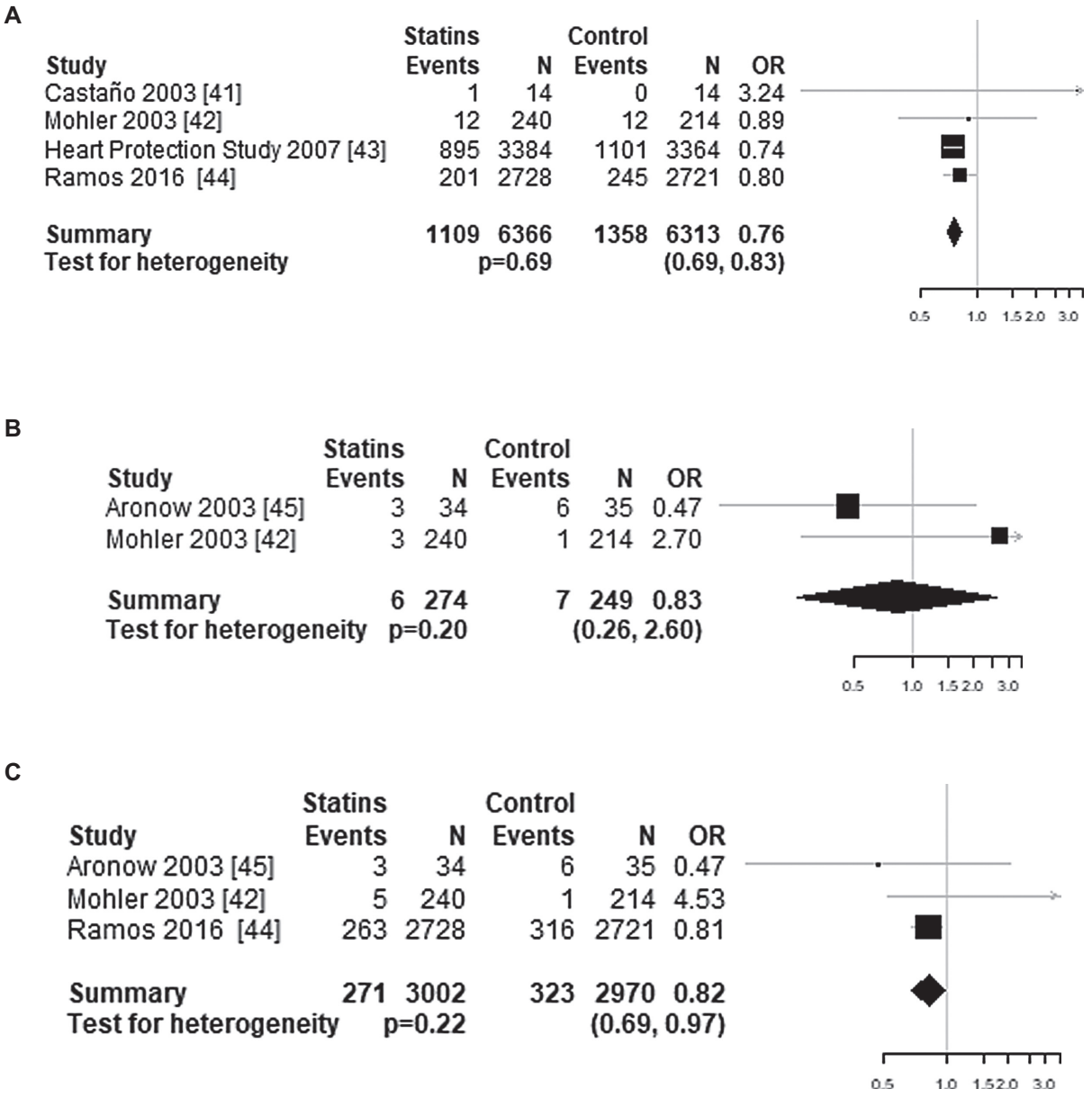


Figure 3. Effect of statin-based treatment on the risk of cardiovascular outcomes and all-cause mortality in patients with PAD. Meta-analysis of randomized controlled trials of statin therapy, showing the effects of statin-based treatment on risk for MACE (A), cardiovascular death (B) and all-cause mortality (C). Analyses based on data in Castano et al. [41], Mohler et al. [42], Heart Protection Study Collaborative Group et al. [43], Ramos et al. [44] and Aronow et al. [45]. (A) Effect of statin-based treatment on risk for MACE. (B) Effect of statin-based treatment on risk of cardiovascular death. (C) Effect of statin-based treatment on risk of all-cause mortality.

follow-up were less likely to be on statin therapy (79% vs. 100%, p=0.04), and had a significantly higher baseline atheroma score (17.6±11.2 vs. 10.7±5.1, p=0.043) [49].

Walking performance

Statin treatment was also shown to favourably impact walking performance in PAD patients with claudication. In one meta-analysis, maximal walking distance for patients on lipid-lowering therapy, notably statins, improved more than that reported with vasodilators, phosphodiesterase and platelet inhibitors (increase by 150 vs. 50 metres) [50]. This benefit increased over time with maximal effect after several months of treatment but was not accompanied by improvement in ABI measurement. Another study showed no difference between patients with claudication doing exercise training treated with atorvastatin versus control, suggesting no added benefit from statin treatment [51].

The effects of statin-based treatment on walking performance were further investigated in the meta-analysis conducted by this Joint Task Force [41, 42, 45, 51, 52]. Two outcomes were evaluated: maximal walking distance and free-pain walking (both duration and distance) on a treadmill. Based on the random-effects model, statin treatment improved walking distance by 45 metres (95% CI: −64.7 to 154.7 metres). There was also improvement in pain-free walking distance and duration (by 15.3 metres [95% CI: −6.8 to 87.5] and 54.9 seconds [95% CI: 40.4–69.3], respectively).

Combination treatment with statin and ezetimibe

Guidelines recommend the addition of ezetimibe if very high-risk patients fail to attain LDL-C goal with maximally tolerated statin therapy. The cardiovascular benefits of this combination therapy is supported by results from IMPROVE-IT (IMProved Reduction of Outcomes:Vytorin Efficacy International Trial), in which ezetimibe on top of simvastatin therapy significantly reduced cardiovascular events (a composite of cardiovascular death, myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization or non-fatal stroke) in patients with ACS (hazard ratio: 0.936; 95% CI: 0.89–0.99; p=0.016) [53]. Subgroup analyses investigated the effects of this combination treatment in patients with polyvascular disease; 1005 (6%) had PAD and 1071 (6%) had stroke or transient ischaemic attack at baseline, with concomitant type 2 diabetes in over one-third [54]. Patients with polyvascular disease were at higher risk, with 7-year Kaplan-Meier cardiovascular event rates 39.8% and 60.0% with concomitant type 2 diabetes versus 29.6% in those with ACS alone.

Although the relative risk reduction associated with ezetimibe plus simvastatin was consistent in patients with or without concomitant polyvascular disease, the absolute benefit was substantially higher in patients with polyvascular disease, especially those with concomitant type 2 diabetes (absolute risk reductions 4.2% and 9.1% vs. 1.7% in those with ACS alone). These translated to a number needed to treat to prevent one event of 24 in patients with polyvascular disease and 11 with concomitant type 2 diabetes versus 59 in those with ACS alone [54]. These findings reinforce the greater cardiovascular benefit from further LDL-C lowering with the combination of ezetimibe and simvastatin.

Combination treatment with statin and a PCSK9 inhibitor

Monoclonal antibodies against PCSK9, i.e., evolocumab and alirocumab, are highly efficacious treatments that reduce LDL-C by 60% on top of statin therapy and are associated with significant reduction in cardiovascular events in outcomes studies in very high-risk populations [55, 56]. Prespecified analyses of these trials have also demonstrated cardiovascular and limb benefit in PAD patients.

What is the evidence that PCSK9 inhibitors, on top of statins, improve outcome in PAD patients?

The FOURIER trial (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial investigated treatment with evolocumab against a background of intense statin therapy (with or without ezetimibe) in 27,564 patients with coronary, cerebrovascular, or peripheral arterial atherosclerosis [55]. A prespecified analysis included 3,642 patients with confirmed lower limb PAD, identified by intermittent claudication and an ABI <0.85, or with a prior peripheral vascular procedure [57]. At the time of randomization, 57% of patients had a history of peripheral revascularization, 3% had undergone amputation, and 69% had an ABI <0.85 and claudication. Almost all were on a statin and 89% were also on antiplatelet therapy. These patients were at higher absolute risk of both MACE and MALE when compared with those with atherosclerosis affecting other vascular beds. Treatment with evolocumab significantly reduced the primary end point (a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization) by 21%, as well as the risk of MALE by 42% [57]. Thus, FOURIER was the first randomized trial to demonstrate that intensive LDL-C lowering decreases the risk of MALE with no safety concerns.

Subsequent analyses of the ODYSSEY OUTCOMES study in 18,924 patients with recent acute coronary syndrome provides further insights [56]. Patients were randomized to alirocumab on top of maximally tolerated statin or statin alone. In those patients who also had PAD (3.2% of the total study population), treatment with alirocumab was associated with 7% reduction in relative risk for the primary endpoint (a composite of coronary heart disease death, nonfatal myocardial infarction, fatal or nonfatal ischaemic stroke, or unstable angina requiring hospitalization) [58]. In patients with atherosclerosis in three vascular territories, the relative risk reduction was substantially higher (by 36% versus 15% for the overall study population) [58]. In a subsequent analysis including all patients with a history of PAD, treatment with alirocumab significantly reduced the risk for PAD events (a composite of critical limb ischaemia, limb revascularization, and amputation for ischaemia) by 41%, corresponding to an 8.6% absolute reduction in risk at 3 years. Notably, the ODYSSEY OUTCOMES Study Investigators identified baseline Lp(a) but not LDL-C concentration as a predictor of the reduction in risk for PAD events with alirocumab [59].

Finally, combined analysis of both trials conducted by this Joint Task Force showed that treatment with a PCSK9 inhibitor, on top of maximally tolerated statin therapy, was associated with a significant 24% reduction in cardiovascular events (odds ratio 0.76, 95% CI: 0.64–0.91), although the difference in all-cause mortality did not achieve statistical significance (odds ratio 0.85, 95% CI: 0.67–1.09) [57, 58].

How to manage muscle adverse effects with statins

Beyond efficacy, the adverse effects of statin therapy, notably perceived or reported muscle pain and cramping, merit consideration in the setting of PAD, given their potential detrimental impact on treatment compliance. Statin associated muscle symptoms (often referred to as SAMS) cover a broad range of clinical presentations, including pain or itching, stiffness, tenderness or cramping,

and may affect about 15–20% of patients, more frequently women than men [60, 61]. Clinical presentation of muscle symptoms is highly heterogenous, although muscle pain and weakness are usually symmetrical and proximal and affect large muscle groups including the thigh, buttock, calves, and back muscles, typically occurring 4–6 weeks after starting treatment [62]. The risk of muscle pain with statins is increased in patients aged over 80 years, as well as those with a smaller body frame, excessive alcohol intake, or hypothyroidism. The onset of new symptoms may occur with an increase in statin dose or after initiation of an interacting drug [63]. People who have exercised regularly before taking statins are less likely to experience muscle pain.

The underlying mechanisms of muscle pain in statin users are not completely elucidated. Preclinical studies showed that statins decrease mitochondrial function, attenuate energy production and alter muscle protein degradation. Additionally, statins cause spontaneous and irregular leaks of calcium from storage within muscle cells and provoke muscle contraction; unregulated calcium leak may also cause damage to muscle cells leading to muscle pain and weakness [64].

SAMS significantly contribute to very high discontinuation rates of statin therapy (up to 75%) [65]. Anecdotally, this proportionally affects many patients with PAD who already have muscle problems in the legs. Treatment non-adherence may have a marked impact on the cardiovascular benefits of statin treatment. In one meta-analysis, patients who were adherent to statin treatment had a 15% lower risk of cardiovascular events compared with those with low adherence [66]. To overcome SAMS, the use of an alternative statin which is metabolised via different hepatic cytochromes is generally recommended, for example the use of rosuvastatin instead of atorvastatin or simvastatin or vice versa.

SAMS are manageable; studies indicate that 90% of patients reporting muscle symptoms are able to tolerate an alternative statin [67]. Another recommended approach is the combination of the maximally tolerated statin dose and a non-statin lipid-lowering therapy such as ezetimibe to attain LDL-C goal.

Conclusions

Taken together, the available literature shows that patients with PAD are at very high cardiovascular risk and should be targeted to achieve guideline-recommended LDL-C goal. Statin-based treatment has been shown to substantially reduce the risk of MACE and MALE by about 25%. The addition of a PCSK9 inhibitor further decreases this risk. Statin-based treatment has also been associated with improved walking performance, including maximum walking distance, and pain-free walking distance and duration.

Perceived or reported muscle symptoms should be assessed and every effort made to ensure that the patients remain on lipid-lowering therapy. Recommended strategies include the use of a lower statin dose combined with a non-statin lipid-lowering therapy such as ezetimibe to attain LDL-C goal.

Antithrombotic therapies in PAD

What can we learn from genetic studies?

Patients with PAD are at high risk of MACE and MALE due to underlying atherothrombotic disease. Genetic studies provide novel insights into thrombotic factors associated with this risk. A genome-wide association study of PAD patients and controls of the MVP (discussed previously) identified a new PAD risk variant in Factor V (Factor V Leiden) that was uniquely associated with PAD, but not other vascular beds. The association of this variant with PAD risk increased with disease severity and was highest with PAD related amputation (odds ratio 1.62) [25]. Given that Factor V Leiden is the most common cause for inherited thrombophilia, this finding underlines the prominent role of thrombosis in the pathogenesis of PAD. Another study showed that CLI in PAD patients was associated with thrombotic luminal occlusion in the absence of advanced atherosclerosis [68]. Furthermore, the close functional relationship between Factor V and Factor Xa in the coagulation cascade supports preventive approaches targeting Factor Xa, as illustrated by the COMPASS trial with the combination of low-dose rivaroxaban and aspirin versus aspirin alone [69].

What is the evidence that antithrombotic therapy reduces MACE and MALE in PAD?

Current management of symptomatic PAD includes antiplatelet monotherapy (either aspirin 75–100 mg daily or clopidogrel 75 mg daily), with improved benefit from more intense antiplatelet therapy [12, 70, 71]. The Antithrombotic Trialist Collaboration study in 6,200 patients with intermittent claudication demonstrated significant reduction in MACE with antiplatelet therapy (most commonly aspirin) versus control (6.4% vs. 7.9%) [72]. A subsequent post hoc analysis of the CAPRIE trial (n=6,452) showed that clopidogrel was superior to aspirin in patients with clinical PAD, with significant reductions in cardiovascular mortality (hazard ratio: 0.76, 95% CI: 0.64–0.91) and MACE (hazard ratio: 0.78, 95% CI: 0.65–0.93) [73]. Although a post hoc analysis of 3,906 asymptomatic and symptomatic PAD patients included in the CHARISMA trial indicated reduction in myocardial infarction with both aspirin and clopidogrel vs. aspirin monotherapy (hazard ratio: 0.63, 95% CI: 0.42–0.95), this was also associated with a significantly increased risk of bleeding (hazard ratio: 1.99, 95% CI: 1.69–2.34) [74].

Following below-the-knee bypass grafting, dual antiplatelet therapy (DAPT) was shown to reduce the primary efficacy endpoints (composite of index-graft occlusion or revascularization, above-ankle amputation of the affected

Recommendation 1. Statins, at the highest tolerated dose, are indicated in patients with PAD for the prevention of cardiovascular events.

Recommendation 2. Low-density lipoprotein cholesterol (LDL-C) should be lowered to <1.4 mmol/L (<55 mg/dL) and by >50% if pre-treatment values are 1.8–3.5 mmol/l (70–135 mg/dL).

Recommendation 3. Combination treatment with a statin and ezetimibe may be considered to improve LDL-C goal attainment. This approach could allow better tolerance of a lower dose of statin in patients with statin side effects.

Recommendation 4. A PCSK9 inhibitor should be added if LDL-C levels remain 50% higher than goal despite statin treatment, with or without ezetimibe.

Recommendation 5. Antiplatelet therapy is indicated to prevent further cardiovascular events. This should be either clopidogrel 75 mg/day, or the combination of aspirin 100 mg/day and rivaroxaban (2 x 2.5 mg/day).

Recommendation 6. Dual antiplatelet therapy (DAPT) should be given for at least one month after drug coated balloon angioplasty, and for 3 months after either drug eluting or covered stent implantation.

Recommendation 7. Based on results from the VOYAGER study, combination therapy with aspirin (100 mg/day) and rivaroxaban (2 x 2.5 mg/day) should be considered for DAPT post-intervention.

Figure 4. Recommendations of the European Atherosclerosis Society/European Society of Vascular Medicine Task Force for the management of PAD patients.

limb, or death) in patients receiving a prosthetic but not venous graft [75]. In patients with stent implantation, prolonged DAPT should be considered with a recent acute coronary syndrome and/or percutaneous coronary intervention (<1 year), stenting of the last patent coronary artery, and multiple coronary vessel disease in diabetes patients with incomplete revascularization. In support, the PRODIGY trial demonstrated benefit with prolonged DAPT (24 months vs. 6 months) after acute coronary syndrome only in patients with concomitant PAD (hazard ratio: 0.54, 95% CI: 0.31–0.95) [76]. Additionally, the PEGASUS-TIMI 54 trial demonstrated that DAPT (ticagrelor plus aspirin) in stable patients with prior myocardial infarction (1–3 years) significantly reduced the risk of MALE (acute limb ischaemia and peripheral revascularization) in a subgroup of patients with PAD (hazard ratio: 0.65, 95% CI: 0.44–0.95) [77].

While plasma coagulation is also implicated as a contributor to peripheral events, trials of therapeutic anticoagulation using vitamin K antagonists in PAD patients showed little benefit and caused increased bleeding. Inhibition of thrombin generation with a low dose Factor Xa inhibitor added to antiplatelet therapy can reduce ischaemic risk, as demonstrated by the COMPASS trial in patients with stable CAD or PAD [69, 78]. The combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg once daily reduced the risk of MACE by 28% (hazard ratio: 0.72, 95% CI: 0.57–0.90), as well as limb events, including MALE by 46% (hazard ratio: 0.54, 95% CI: 0.35–0.84), acute limb ischaemia by 44% (hazard ratio: 0.56, 95% CI: 0.32–0.99), and MALE plus major amputation by 46% (hazard ratio: 0.54, 95% CI: 0.35–0.82). There was, however, an increase in major bleeding but not fatal or critical organ bleeding (hazard ratio: 1.61, 95% CI: 1.12–2.31). Thus, the COMPASS trial demonstrated for the first time that antithrombotic treatment in patients with PAD reduces both MACE and MALE, including amputation, although at the risk of increased bleeding [79].

Finally, VOYAGER PAD compared rivaroxaban 2.5 mg twice daily plus aspirin and aspirin alone in 6,564 PAD patients who had undergone lower-extremity revascularization [80]. The primary efficacy outcome was a composite of acute limb ischaemia, major amputation for vascular causes, myocardial infarction, ischaemic stroke or cardiovascular death. Three-year Kaplan-Meier estimates showed a significant 15% reduction in the primary outcome in the rivaroxaban group (17.3% vs. 19.9% with placebo, hazard ratio: 0.85, 95% CI: 0.76–0.96; p =0.009). The absolute risk reduction was 1.5% at 6 months, 2.0% at one year and 2.6% at 3 years. While TIMI major bleeding did not differ significantly between the groups, the incidence of ISTH (International Society on Thrombosis and Haemostasis) major bleeding was significantly higher with rivaroxaban and aspirin than with aspirin alone. It was

estimated that for every 10,000 patients treated for one year, rivaroxaban 2.5 mg twice daily added to aspirin would prevent 181 primary efficacy outcome events at the cost of 29 principal safety outcome events [80].

Taken together, the results from the VOYAGER PAD trial complement and extend findings from the COMPASS trial. Thus, for patients with extensive PAD, especially those who have undergone revascularization for PAD, addition of rivaroxaban to the treatment regimen may be considered weighing concomitantly the bleeding risk.

Key recommendations

Based on the evidence discussed in this statement, this Joint EAS-ESVM Task Force provides recommendations for the management of PAD patients (Figure 4). Optimal management of dyslipidaemia, together with guideline recommended antithrombotic therapy, are essential to improve the morbidity, disability and mortality of this increasingly prevalent – but underdiagnosed and undertreated – condition.

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Conflict of interest
CB, IB, PPoredos none.
JJFB sits on the PAD Advisory Board of Bayer.
MB is a consultant for Biotronic, Cook Ltd and Boston cientific.
ALC participates in the speaker bureau for Akcea, Amgen, Sanofi, Esperion, Kowa, Novartis, Ionis Pharmaceuticals, Mylan, Menarini, Merck, Recordati, Regeneron, Daiichi Sankyo, Astrazeneca, Aegerion, Amryt, Sandoz. He is a consultant on advisory boards for Akcea, Amgen, Sanofi, Esperion, Kowa, Novartis, Ionis Pharmaceuticals, Mylan, Menarini, Merck, Recordati, Regeneron Daiichi Sankyo, Genzyme, Aegerion, Sandoz. The work of ALC at MultiMedica been supported by Ministry of Health – Ricerca Corrente – IRCCS MultiMedica.
CH has published with Mars, and the Cranberry Institute.
PParini has equity interests in Galmed Pharmaceuticals; has ownership in Lipoprotein Research Stockholm AB; has ownership of patent Japanese Patent No. 2020-011068; is member of the Scientific Advisory Board of Ambys Medicine and of Diaccurate SAS.
LT is Company consultant for Abbott, Amgen, Bayer, MSD, Mylan, Novartis, Sanofi and has participated in a study for Amgen.

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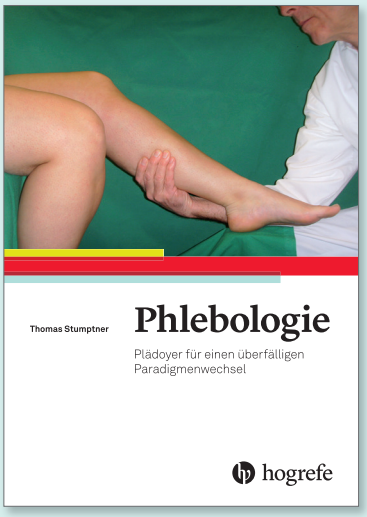
ORCID
Professor Jill Belch
https://orcid.org/0000-0001-8280-6689

Correspondence address
Prof. Jill J. F. Belch for the ESVM
The Institute of Cardiovascular Research
University of Dundee
Ninewells Hospital and Medical School
Dundee DD1 9SY
UK

j.j.f.belch@dundee.ac.uk

Correspondence address
Lale Tokgözoğlu for the EAS
Department of Cardiology
Hacettepe University Faculty of Medicine
06230 Ankara
Turkey

Ursache und Wirkung verstehen



Thomas Stumptner

Phlebologie

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In diesem Buch wird die Komplexität des Beinvenensystems umfassend dargestellt. Funktionsdefizite führen zur Erkrankung mit „Venenstau“ (subfasziales venöses Ödem) und möglichen Folgeerkrankungen wie Nutritionsstörungen bis hin zum Geschwür, der Thrombose oder Krampfadern. Umfassend recherchierte wissenschaftliche Erkenntnisse belegen dieses Konzept und sollen das Verständnis für die Behandlung phlebologischer Erkrankungen fördern.

„Phlebologie“ und „Orthopädie“ sind als funktionelle und anatomisch nachvollziehbare Einheit für den Beinvenenkreislauf zu sehen. Für die individuelle Therapie des einzelnen Patienten muss diese Komplexität der Funktionszusammenhänge beachtet werden.

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Original communication

Effect of ACEI and ARB treatment on nitric oxide-dependent endothelial function

Kangbo Li[1,2], Claudia Zemmrich[3], Peter Bramlage[3], Anja Bondke Persson[2], Mesud Sacirovic[1], Oliver Ritter[4,5], Eva Buschmann[6], Ivo Buschmann[1,5], and Philipp Hillmeister[1,5]

[1] Department for Angiology, Center for Internal Medicine I, Brandenburg Medical School Theodor Fontane, Campus University Clinic Brandenburg, Deutsches Angiologie Zentrum Brandenburg-Berlin (DAZB), Brandenburg an der Havel, Germany
[2] Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Germany
[3] Institute for Pharmacology and Preventive Medicine, Cloppenburg, Germany
[4] Department for Cardiology, Center for Internal Medicine I, Brandenburg Medical School Theodor Fontane, Campus University Clinic Brandenburg, Brandenburg an der Havel, Germany
[5] Faculty of Health Sciences, joint Faculty of the Brandenburg University of Technology Cottbus – Senftenberg, the Brandenburg Medical School Theodor Fontane and the University of Potsdam, Brandenburg Medical School Theodor Fontane, Germany
[6] Department of Cardiology, University Clinic Graz, Austria

Summary: *Background:* Angiotensin-converting-enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) are widely used as a first-line therapy for the treatment of cardiovascular disease. Here, ACEI modulate the bradykinin receptor (BDKRB1 and BDKRB2) system and NO-dependent endothelial function, thus determining cardiovascular health and regenerative arteriogenesis. The current study aims at evaluating nitric oxide-dependent endothelial function, and gene expression of bradykinin receptors in peripheral blood mononuclear cells (PBMC) from patients with ACEI or ARB treatment. *Patients and methods:* The WalkByLab has been established to screen cardiovascular patients for peripheral artery disease and coronary artery disease. In total 177 patients from WalkByLab with heterogenous disease and risk status were randomly selected, divided according to their medication history into the following groups: 1. ACEI group, 2. ARB group or 3. non-ACE/ARB group. Total plasma nitrite/nitrate (NO) levels were measured, endothelial function was evaluated by assessing flow meditated dilation (FMD). PBMC were isolated from peripheral whole blood, and gene expression (qRT-PCR) of bradykinin receptors and angiotensin converting enzyme were assessed. *Results:* Plasma total NO concentration in the ACEI group (24.66±16.28, µmol/l) was increased as compared to the ARB group (18.57±11.58, µmol/l, P=0.0046) and non-ACE/ARB group (16.83±8.64, µmol/l, P=0.0127) in patients between 40 to 90 years of age. However, FMD values (%) in the ACEI group (7.07±2.40, %) were similar as compared to the ARB (6.35±2.13, %) and non-ACE/ARB group (6.51±2.15, %), but significantly negatively correlated with age. Interestingly, BDKRB1 mRNA level was significantly higher and BDKRB2 mRNA level lower in the ACEI group (BDKRB1 3.88-fold±1.05, BDKRB2 0.22-fold±0.04) as compared to the non-ACE/ARB group (BDKRB1 1.00-fold ±0.39, P<0.0001, BDKRB2 1.00-fold±0.45, P=0.0136). *Conclusions:* ACEI treatment enhances total nitrite/nitrate concentration, furthermore, upregulates BDKRB1 in PBMC, but downregulates BDKRB2 mRNA expression. FMD is a strong determinant of vascular aging and is sensitive to underlying heterogenous cardiovascular diseases.

Keywords: flow mediated dilation, nitric oxide, kallikrein-kinin-system, angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers

Introduction

Vascular aging processes impact atherosclerosis risk and arteriogenic remodelling capacity and are most commonly analyzed by measuring peripheral blood mononuclear cells (PBMCs) phenotype and endothelial function [1]. Whereas atherosclerosis and arterial occlusion are the consequence of most vascular aging processes, regenerative arteriogenesis is the primary compensatory mechanism against ischemic vascular disease (CAD, PAD). Arteriogenesis is one of the key mechanisms of protective vascular growth, and involves the remodeling and positive outgrowth of

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pre-existing collateral arteries following a stenosis or arterial occlusion [2]. For arteriogenesis it was shown as well that endothelial function and PBMCs play a critical role in endothelial proliferation, intima formation and maturation of collateral arteries [3, 4]. Thus, where vascular regeneration interacts positively with PBMC phenotypes and endothelial function, these factors are negatively influenced by pathological processes of aging, and determine the severity of diseases. Recent research has shown that in terms of vascular regeneration, PBMC activity and endothelial function are linked through bradykinin receptor signaling and NO production [1, 5]. In regard to vascular diseases, Angiotensin-converting-enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) are cornerstones of the pharmacological therapy for patients with coronary artery disease (CAD), peripheral artery disease (PAD), heart failure (HF) and essential hypertension [6, 7, 8, 9]. Furthermore, ACEI and ARB are discussed to be involved in arteriogensis and vascular regeneration. Therefore, in this work, we investigate whether ACEI and ARB therapy is associated with bradykinin receptor signaling in PBMCs, NO production, and endothelial function.

Beyond the property that angiotensin-converting enzyme (ACE) inhibitors are used to treat hypertension and ischemic heart disease, many research groups are looking at the bradykinin-mediated aspects of ACE inhibition [10]. Angiotensin-converting enzyme (ACE, also known as kininase II) is the key enzyme for the degradation of bradykinin (BK). BK is one of the major endothelium-dependent vasodilators in cardiovascular homeostasis. Therefore ACEI, the inhibitor of ACE, prevents BK degradation and leads to the BK mediated and endothelium-dependent vasodilation (EDV) [11]. Furthermore, our group was the first to demonstrate that bradykinin receptor signaling is a strong modulator of therapeutic arteriogenesis [4]. Research has shown that ACEI can be regarded as the allosteric enhancer of bradykinin receptors. The bradykinin receptor family consists of two G protein-coupled receptors: bradykinin receptor 1 (BDKRB1) and bradykinin receptor 2 (BDKRB2), whereby ACEI are agonists activating BDKRB1 directly on the extracellular loop and also indirectly activating the ACE/BDKRB2 heterodimer by altering conformational change [12]. Bradykinin receptor BDKRB2 is constitutively expressed in various cell types, whereas bradykinin receptor BDKRB1 is only upregulated under the inflammatory conditions. BK and kallidin, derived from plasma and tissue kallikrein, respectively, are the corresponding ligands of BDKRB2, whereas the BK and kallidin derivatives des-Arg9-bradykinin and Lys-bradykinin are the corresponding ligands of BDKRB1 [13]. It was shown that BDKRB2 and BDKRB1 signaling induces nitric oxide (NO) production in endothelial cells and circulating immune cells [14]. Hence, bradykinin receptors and NO are major players in mediating arteriogenesis and endothelial function [5].

In addition to ACEI, ARB are recommended as first-line treatment options for hypertension. ARB are superior to ACEI in regard to their more favorable (drug) safety profile ARB selectively inhibit angiotensin II type 1 receptors (AT1), thereby augmenting angiotensin II type 2 receptor (AT2) activity, whose effects antagonize AT1 [15, 16]. Interestingly, a functional heterodimerization of AT2-BDKRB2 enhances peptide ligand binding and receptor activation [17]. Animal experiments also demonstrated that angiotensin II induced upregulation of BDKRB1 is abrogated in AT1 knockout mice. BDKRB1 can be regarded as the downstream target of AT1 agonists [18].

In the current study we therefore analyze total nitrite/nitrate concentration in plasma, endothelial function by flow mediated dilation and gene expression of bradykinin receptors and angiotensin converting enzyme in PBMCs from patients with CAD, PAD, cerebrovascular disease (CVD), and hypertension treated pharmacologically with either ACEI or ARB.

Patients and methods

Study population

In total 177 patients with atherosclerotic disease (CAD, PAD, CVD) were randomly selected from the WalkByLab-Registry database. These are the patients who presented to the WalkByLab center Brandenburg/Havel (Brandenburg Clinic, Brandenburg Medical School) Germany in the period from July 2019 to February 2020 with the corresponding pre-existing cardiovascular disease. The WalkyByLab aims to interdisciplinarily screen, diagnose and follow-up patients with cardiovascular disease (www.lauflab.de). The WalkByLab register trial protocol was reviewed and approved by the ethical committee of the Cottbus Medical Association (Landesärztekammer Cottbus, study number of the ethics committee: AS 74(bB)/2018). The screening trial is performed in accordance with the principles of the declaration of Helsinki.

Isolation of peripheral blood mononuclear cells

15 ml blood was collected in three vacutainer EDTA tubes (Becton Dickinson) by routine venipuncture procedure. Blood was diluted 1:1 in PBS, and carefully layered onto the Ficoll-Paque density gradient media (GE Healthcare) at a ratio of 4:3 and centrifuged at 400 g for 25 min. The upper layer of plasma was collected from each sample and frozen in 2 ml aliquots at −80 °C until use for determination of total nitrite/nitrate levels.

The middle layer containing PBMCs was transferred to 50 ml sterile tubes, and washed twice with 40 ml PBS. Cell counting was performed under the microscope. Aliquots including 5 million cells were centrifuged at 1500 g for 10 minutes and the pellet was frozen and stored at −80 °C until use for RNA isolation.

RNA isolation and quantitative real-time PCR-based analysis

Total RNA was extracted from PBMCs by using the Trizol reagent (Thermo Fisher Scientific) according to the manufacturer's instructions. RNA integrity was assessed by agarose gel electrophoresis, quantitative analysis of RNA was performed using Qubit® RNA BR assay together with the Qubit® 3.0 Fluorometer (Thermo Fisher Scientific). 1 µg total RNA was used for the first strand cDNA synthesis by using QuantiTect Reverse Transcription Kit (QIAGEN). Samples were deployed in the peqSTAR thermal cycler (VWR International). The mRNA levels of the target gene were analyzed by real-time polymerase chain reaction using the LightCycler® 96 Real-Time PCR System (Roche). Each reaction system contained 1 µl cDNA, 2 µl primer working solution, 7 µl RNase/DNase-free water and 10 µl QuantiTect® SYBR® Green PCR Kit (QIAGEN). All the primers were synthesized and purchased from Eurofins Genomics Germany GmbH. All samples were run in duplicate (Table I).

Determinations of total nitrite/nitrate levels in plasma

In the cell, nitric oxide is converted into nitrite and nitrate as the stable metabolites after a series of reactions. Therefore, total nitrite/nitrate concentration is the best value for assessing the NO production in a physiological system. Plasma samples were thawed and ultrafiltered to remove hemoglobin by centrifugation in an ultra-0.5 centrifugal filter devices (Merck Millipore). Total nitrite/nitrate levels in plasma were determined according to the manufacturer's instructions (Cayman Chemical). In brief, conversion of nitrate to nitrite is achieved by utilizing nitrate reductase enzyme. During this process a deep purple azo dye is formed based on Griess reagent, and the light absorbance can be spectrophotometrically measured at 548 nm on a Spark multimode microplate reader (Tecan Group AG).

Assessment of flow mediated dilation

The AngioDefender (Everist Health) medical device was used to evaluate endothelial function by assessing flow mediated dilation (FMD) of the brachial artery. FMD measurement is regarded as the gold standard method for evaluation of endothelial function. The novel Angio Defender medical device allows for a precise, standardized, and automated measurement of FMD-value by oscillation technique, it has been proven to show less measurement errors when compared with classical FMD measurement based on ultrasound techniques. The AngioDefender measurement technique is therefore regarded superior to the classical measuring methods.

Treadmill testing

A treadmill and the "Gardner Test Protocol" are used to determine the maximum walking distance. The test is performed under the supervision of a physician, the patient is secured with a drop stop device (safety bar with chest harness). The patient initially stands on the lateral treads and the natural walking speed is tested, while the treadmill accelerates to 3.2 km/h to allow the patient to enter the treadmill and start the test (time "zero"). Subsequently, the incline angle of the treadmill changes by 2 degrees every 2 minutes. In addition to this, the concomitant symptoms (peripheral fatigue, angina pectoris, dyspnea and others) during treadmill testing have also been recorded. However, some patients did not participate to the walking test because they suffered severe cardiovascular disease. Hence, we have results from in total 83 patients of the here analyzed patient population.

Statistical analysis

Data of demographics, plasma nitrite level and flow mediated dilation are given as mean±standard deviation (SD), data of mRNA expression are given as mean±standard error of the mean (SEM). A Kolmogorov-Smirnov test was carried out to check the distribution of quantitative variables, data following a normal distribution were analyzed by the one-way analysis of variance (ANOVA), data following a non-normal distribution were analyzed by the Kruskal-Wallis test. A p-value of $P \leq 0.05$ (two-sided) was considered to indicate statistical significance.

Results

All patients were screened for medication history, blood samples were taken, and FMD measured. Patients were divided into three groups as follows according to the medication history: 1. ACEI group, 2. ARB group, and 3. non-ACE/ARB group (neither treated with ACEI or ARB). Population characteristics are presented in Table II.

Patient age groups were 40 to 49 years (2.82%), 50 to 59 years (9.60%), 60 to 69 years (36.72%), 70 to 79 years (31.64%) and 80 to 89 years (19.21%), respectively. The mean age was 70.10 years (SD=9.35). 41.81% patients were female and 58.19% patients were male. The mean BMI of patients was 27.96 (SD=4.95) and of these patients were normal weight (BMI=18.5–23, 27.81%), overweight (BMI= 23.0–27.49, 44.38%), and obese (BMI>27.5, 27.81%), respectively. Common comorbidities included: hypertension (n=167), diabetes mellitus (n=36), renal dysfunction (n=34), hyperlipidemia (n=74). 84 patients suffered from PAD, 91 patients suffered from CAD, and 12 patients suffered from CVD. For 32 patients a history of myocardial infarction was reported, heart failure for 41 patients, 74 were smokers.

Total plasma nitrite/nitrate concentration

Total plasma nitrite/nitrate level in the ACEI group (24.66±16.28, µmol/l) was significantly higher than that

Table I. qRT-PCR primer list (sense and antisense primers)

Gene	Forward (5'-3')	Reverse (5'-3')
BDKRB1	ATTCTCCCACCTCAGCCTCT	CTCTGGTTGGAGGATTGGAG
BDKRB2	CTTCATGGCCTACAGCAACA	GCACACTCCCTGGTACACCT
ACE	ATGAAGACCTGTTATGGGCATGG	ATTTCGGGTAAAACTGGAGGATGG
RPLPO	ACGGGTACAAACGAGTCCTG	AGCCACAAAGGCAGATGGAT

Table II. Population characteristics

	ACEI (n=73)	ARB (n=68)	Non-ACEI/ARB (n=36)	*P*
Demographics				
Gender, male	47	34	22	0.207
Age, y	68.45±9.40	71.85±9.09	70.11±9.38	0.097
BMI, kg/m^2	27.94±5.34	28.62±5.11	26.69±3.45	0.181
Medical history				
Hypertension	67	67	33	0.164
Diabetes mellitus	16	12	8	0.781
Renal dysfunction	12	13	9	0.566
Hyperlipidemia	32	30	12	0.513
PAD	38	30	16	0.590
CAD	38	33	20	0.784
CVD	6	4	2	0.814
Myocardial infarction	8	16	8	0.118
Heart failure	18	16	7	0.828
PCI/PPI	27	28	18	0.431
CABG/PABG	8	10	1	0.174
Smoking	28	28	18	0.506
Medication history				
Beta-blocker	42	38	23	0.725
Calcium channel blockers	22	33	7	0.007
Diuretics	31	24	6	0.028
Statins	46	45	23	0.924
Aspirin	36	42	16	0.169
Antidiabetics	10	9	4	0.928
Insulin	6	5	3	0.977

PCI: Percutaneous coronary intervention, PPI: percutaneous peripheral interventional, CABG: coronary artery bypass grafting, PABG: peripheral artery bypass grafting.

in the ARB group (18.57±11.58, µmol/l, *P*=0.0046) and non-ACE/ARB group (16.83±8.64 µmol/l, *P*=0.0127) (Figure 1A). The plasma total nitrite/nitrate level in the ARB group showed a similar concentration (18.57±1 1.58, µmol/l) as compared to the non-ACE/ARB group (16.83±8.64 µmol/l).

Furthermore, plasma nitrite/nitrate levels were analyzed in regard to possible sex differences in the medical treatment groups, however results showed no relation between plasma nitrite/nitrate and sex (*P*=0.963) (Figure 1B). A Spearman's rank correlation was calculated in order to investigate how plasma total nitrite/nitrate is related to the different medical treatment groups in the context with age. Nitrite/nitrate was not correlated with age in any group (*P*=0.215) (Figure 1C).

Endothelial function analyzed by flow mediated dilation (FMD)

Cardiovascular health and arteriogenic capacity are largely determined by arterial endothelial function. Endothelial function was assessed in all patients using the AngioDefender, which is a new and standardized method for determining FMD. FMD in the ACEI group (7.07±2.40, %) showed values with no significant differences as compared to the ARB group (6.35±2.13, %) and values were comparable to the non-ACEI/ARB group (6.51±2.15, %) (Figure 2A). FMD was analyzed in regard to possible sex differences and results showed no relation between FMD and gender (*P*=0.229) (Figure 2B). Correlation analysis of FMD with age showed a significant and negative correlation. FMD

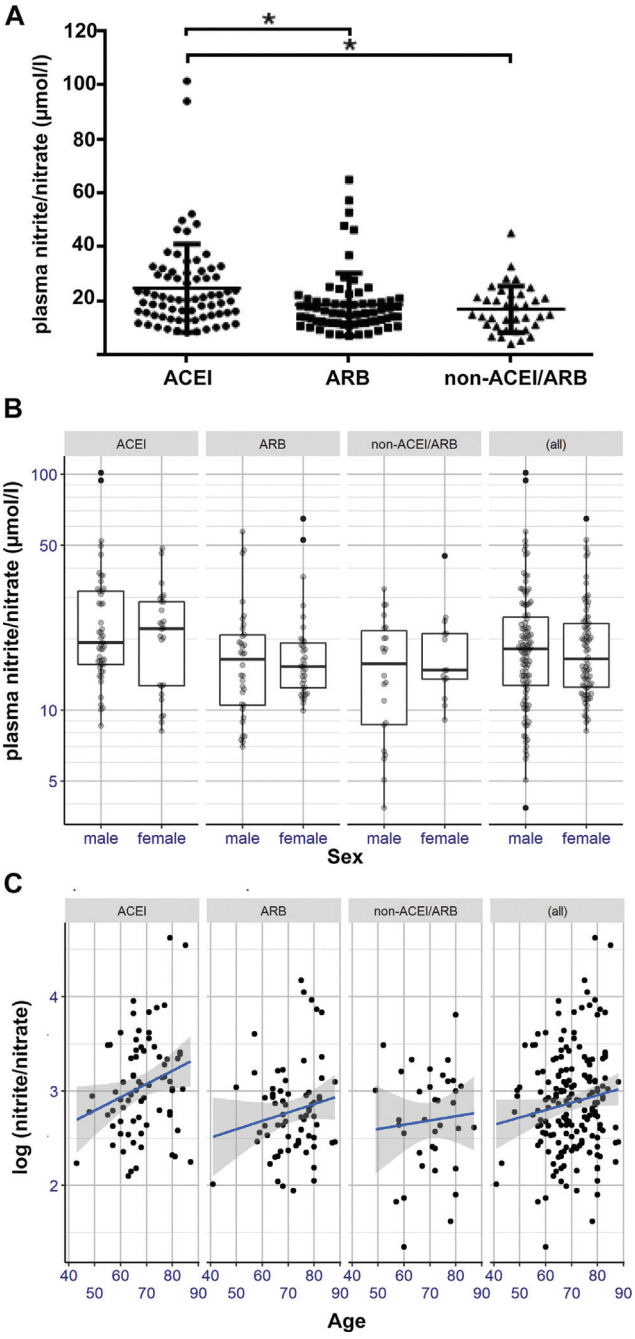

Figure 1. (A) Plasma total nitrite/nitrate levels in patients of three groups (*$P \leq 0.05$). (B) Correlation analysis between plasma total nitrite/nitrate levels and gender shows no correlation. (C) Correlation analysis between plasma total nitrite/nitrate levels (log scale) and age shows no correlation. ACEI (n=73), ARB (n=68), non-ACEI/ARB (n=36).

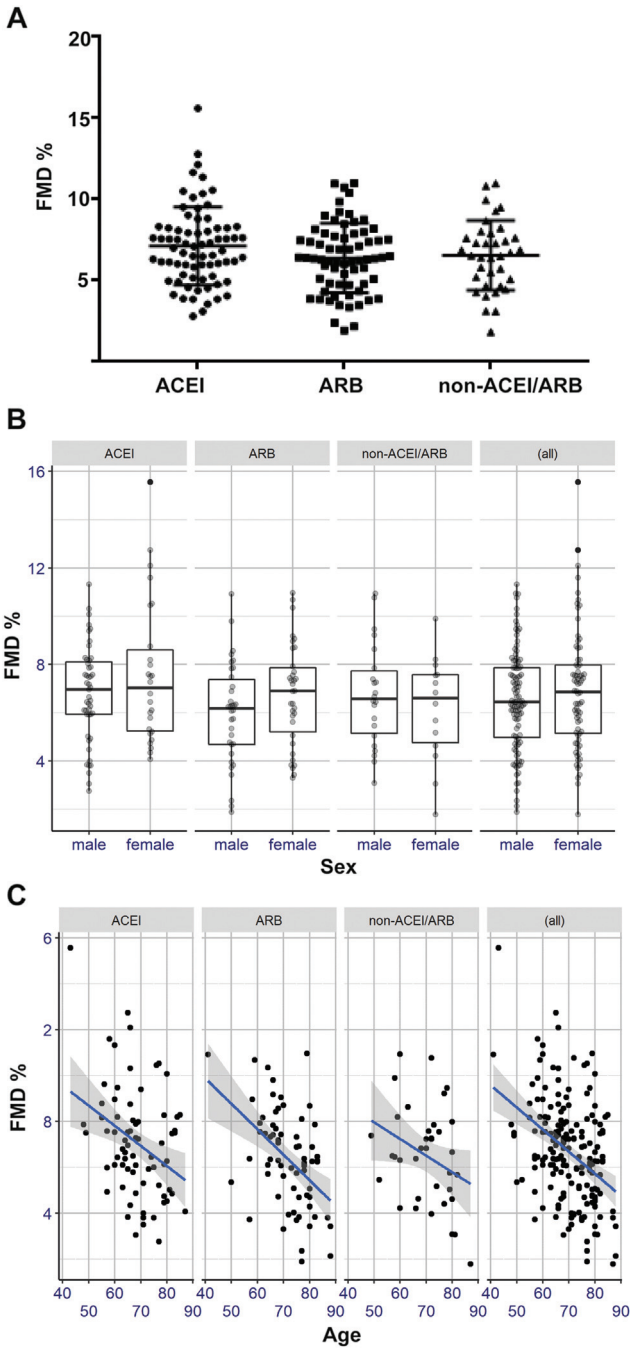

Figure 2. (A) FMD of the brachial artery in patients of three groups. (B) Correlations analysis between FMD and gender shows no correlation. (C) FMD correlates with age in all treatment groups (linear model). ACEI (n=73), ARB (n=68), non-ACEI/ARB (n=36).

decreases with increasing age in all medical treatment groups ($P<0.001$) (Figure 2C). Furthermore, FMD does not correlate with nitrite/nitrate level in any medical treatment group ($P=0.949$) (Figure 3A, Table III)

Treadmill testing

Treadmill testing results showed that the maximal walking distance and walking speed in the ACEI are slightly higher than in the ARB group and slight lower than in the non-ACEI/ARB but without significant differences. The results of concomitant symptoms reported during treadmill testing showed there is no significant differences between three groups groups (Table IV).

Gene expression analysis of markers and regulators of arteriogenesis

ACEI treatment resulted in an upregulation of BDKRB1 in PBMCs, but a downregulation of BDKRB2 mRNA expression. BDKRB1 mRNA level was significantly higher in the ACEI group (3.88-fold±1.05), when compared to non-ACE/ARB group (1.00-fold±0.39, $P<0.0001$). The expression level of BDKRB1 in the ARB group (2.46-fold±0.59)

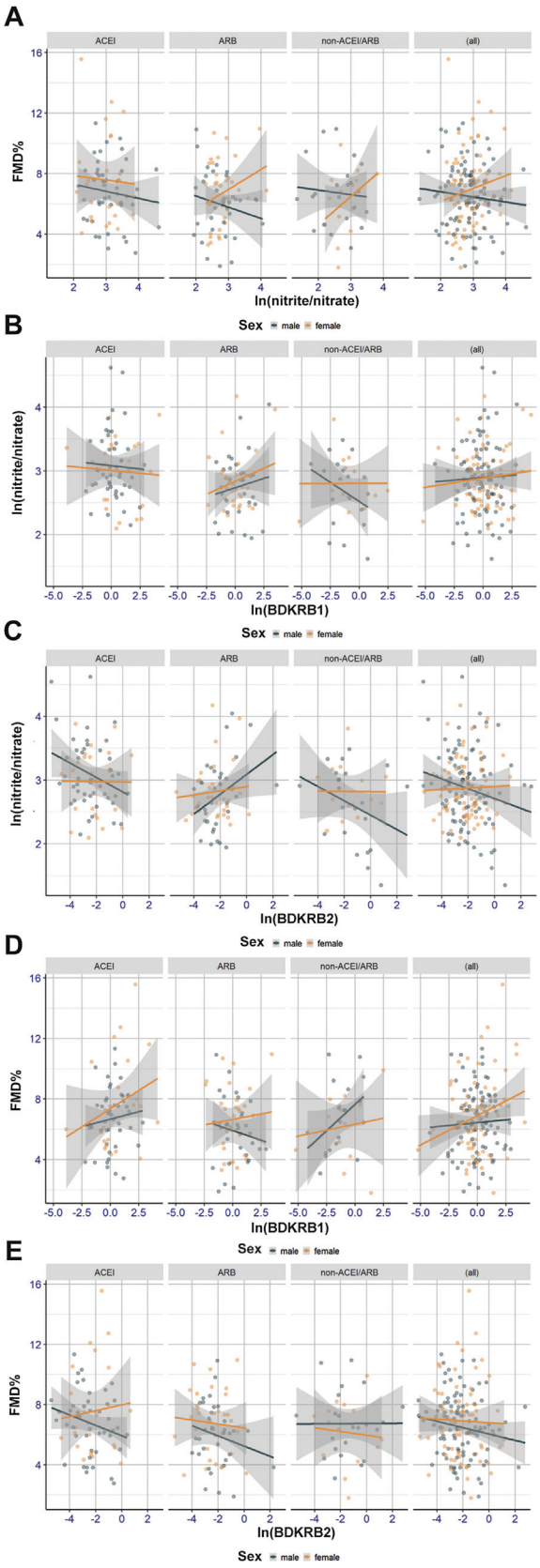

Figure 3. Correlations analyses between FMD, plasma total nitrite/nitrate levels and gene expression of BDKRB1/BDKRB2.

was slightly lower than in the ACEI group, but significantly higher as compared to the non-ACE/ARB group (1.00-fold ±0.39, *P*=0.0003) (Figure 4A). Regarding BDKRB2, the mRNA expression level in the ACEI group (0.22-fold ±0.04) was significantly lower than in the non-ACE/ARB group (1.00-fold±0.45, *P*=0.0136). Again, the ARB group (0.32-fold±0.14), follows the same trend as the ACEI group, was slightly higher than ACEI group, but it is significantly lower as compared to the non-ACE/ARB group (1.00-fold±0.45, *P*=0.0228) (Figure 4B). Finally, the ACE mRNA level was unchanged between all groups, ACEI group (0.63-fold±0.06), ARB group (0.69-fold±0.08), and non-ACE/ARB group (1.00-fold±0.30) (Figure 4C).

In the context of previously described total plasma nitrite/nitrate concentration and flow mediated dilation, we performed a correlation analysis in relation to bradykinin receptor BDKRB1 and BDKRB2 gene expression. The correlation analyses showed that FMD positive correlates with BDKRB1 in female patients (*P*=0.040), however, plasma nitrite/nitrate concentration does not correlate neither with BDKRB1 nor with BDKRB2 (Figure 3, Table III).

Discussion

This work demonstrates that ACEI, as compared to ARB treatment and non-ACEI/ARB treatment, is effective in increasing the plasma total nitrite/nitrate concentration, with concomitant BDKRB1 upregulation and BDKRB2 downregulation in circulating PBMCs of patients with heterogeneous ischemic vascular disease. However, although NO metabolism was elevated in the ACEI treatment group, endothelial function as measured by FMD remained unchanged as compared to the ARB and Non-ACEI/ARB group, respectively. Furthermore, this study compared nitrite/nitrate levels and FMD to age and demonstrated that FMD but not nitrite/nitrate negatively correlates with age.

Nitrite/nitrates are viewed as the end metabolites of nitric oxide (NO), which is the primary vasodilator molecule and the secondary messenger of the bradykinin receptor signaling pathway. NO not only plays an important role for modulating endothelium-dependent relaxation, but also for regulating active vascular growth [19]. Previous research indicated the superiority of ACEI over ARB with regard to their effect on NO production [20, 21]. In-vivo studies have shown that the nitric oxide synthesis (NOS) inhibitor – L-NAME (N(gamma)-nitro-L-arginine methyl ester) causes an overactivation of the renin–angiotensin system (RAS), thereby leading to hypertension. However, ACE knockout mice are resistant to the hypertension induced by L-NAME [22]. Furthermore, administration of ACEI decreased serum asymmetric dimethylarginine, which is an endogenous NOS inhibitor [23, 24]. These results demonstrate that inhibition of ACE is an important and targeted molecular therapeutic option to upregulate NO levels. These publications are consistent with our finding regarding ACEI treatment elevated plasma NO levels. However, in this study we show for the first time an elevated plasma NO level in hypertensive, ACEI treated patients with different and heterogeneous ischemic vascular diseases (CAD, PAD and CVD). The elevated

Table III. Correlation analyses

	ACEI (n=73)		ARB (n=68)		Non-ACEI/ARB (n=36)		Total sample (n=177)	
	Male	Female	Male	Female	Male	Female	Male	Female
FMD_nitrite/nitrate								
r	−0.125	−0.051	−0.190	0.267	−0.087	0.358	−0.096	0.157
P	0.402	0.805	0.282	0.126	0.700	0.210	0.336	0.181
FMD_BDKRB1								
r	0.109	0.280	−0.143	0.078	0.416	0.128	0.046	0.246
P	0.476	0.175	0.442	0.672	0.076	0.678	0.657	0.040
FMD_BDKRB2								
r	−0.235	0.085	−0.198	−0.079	0.004	−0.086	−0.149	−0.032
P	0.120	0.688	0.261	0.663	0.986	0.769	0.137	0.787
Nitrite/nitrate_BDKRB1								
r	−0.042	−0.061	0.138	0.217	−0.304	0.001	0.037	0.097
P	0.782	0.774	0.461	0.233	0.206	0.996	0.724	0.425
Nitrite/nitrate_BDKRB2								
r	−0.042	−0.061	0.138	0.217	−0.304	0.001	−0.193	0.034
P	0.782	0.774	0.461	0.233	0.206	0.996	0.053	0.775

Table IV. Parameters of treadmill test

	Maximal walking distance (m)	Duration (mm:ss)	Walking speed (m/h)	Peripheral fatigue	Angina pectoris	Dyspnea	Others
ACEI (n=34)	257.97±192.16	05:13±03.55	3036.21±427.65	8	3	28	6
ARB (n=38)	250.37±175.52	05:06±03:31	2966.95±581.42	14	1	28	5
Non-ACEI/ARB (n=11)	298.73±177.90	05:44±03:28	3174.09±162.97	4	0	5	2
P	0.741	0.880	0.453	0.443	0.343	0.055	0.846

nitrite/nitrate levels found in this study have interesting scientific implications, NO is the most important molecule for the regulation of vascular tone, but also plays a crucial role (I) in modulating endothelial function, and (II) in regulating arteriogenesis [1, 5].

With regard to endothelial function, recent studies have suggested that endothelial dysfunction precedes the progression of atherosclerosis and other age-related vascular diseases. Therefore, endothelium-dependent FMD can be regarded as a prognostic indicator of major adverse cardiovascular and cerebrovascular events (MACCE) [25]. Indeed, studies measuring FMD in patients with cardiovascular disease showed that endothelial dysfunction correlates to CAD severity [26]. Furthermore, both pre-clinical studies and clinical trials have clearly illustrated that ACEI could improve FMD and prevent endothelial dysfunction [27, 28]. However, an ACEI related FMD improvement was not confirmed in this analysis. FMD is slightly increased in the ACEI treatment group as compared to the ARB treatment group, but this value is not significantly different. The reason for our deviating findings probably depends on the selection of patients with different underlying cardiovascular diseases. Endothelial function precisely maps biological age, but is also very sensitive to different forms of cardiovascular diseases. Therefore, selection of a heterogeneous group of patients with different cardiovascular diseases could affect endothelial function differently. Nevertheless, there was a clear negative correlation of FMD with patient age. Indeed, numerous studies have shown that progressive endothelial dysfunction is one of the most important aging-associated determinants [29, 30], and we confirmed that FMD is strongly and negatively correlated with increasing age. Since, we enrolled the patients in a randomized manner, the number of males and females differed by 58.19% to 41.81%. We therefore also investigated the differences in nitrite/nitrate levels and FMD between males and females. In our analysis there were no differences in nitrite/nitrate levels and FMD related to gender, thus different gender ratios within our patient group should not bias the group differences discussed herein.

In addition, our results show for the first time that patients on ACEI medication have upregulated BDKRB1, but downregulates BDKRB2 mRNA expression in PBMCs. ACEI not only inhibit angiotensin I (Ang I) to angiotensin II (Ang II) conversion, but also increase bradykinin concentration. Bradykinin derivatives are direct ligands of BDKRB2 and BDKRB1. In fact, stimulation of BDKRB2 leads to intracellular activation of endothelial nitric oxide synthase (eNOS) in the endothelia cell layer, and stimulation of BDKRB1 results in activation of inducible nitric oxide synthase (iNOS) in immune cells, such as PBMCs

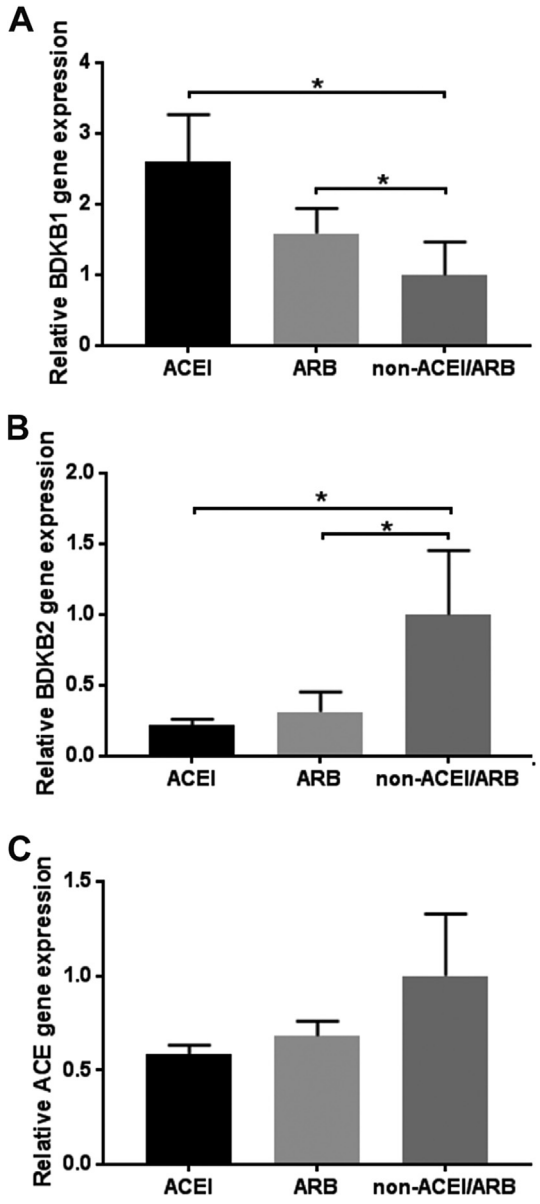

Figure 4. Gene expression of BDKRB1: ACEI (n=70), ARB (n=63), non-ACEI/ARB (n=32), gene expression of BDKRB2: ACEI (n=70), ARB (n=67), non-ACEI/ARB (n=36), and gene expression of ACE: ACEI (n=72), ARB (n=68), non-ACEI/ARB (n=36) in PBMC (*$P \leq 0.05$).

[14]. Previous research has also shown that the antagonist of BDKRB2 attenuated the augmentation of NO production induced by ACEI. While BDKRB2s are known to regulate vascular tone, they also exhibit atherogenic activity by increased reactive oxygen species generation [31]. In contrast, BDKRB1s exhibit anti-atherosclerotic activities, and mice deficient in kinin B1 receptor and apolipoprotein E showed a predisposition to atherosclerosis development [32]. Recent research shows that both of BDKRB1 and BDKRB2 can respectively bind to different heterotrimeric G proteins and thereby increase NO production by activing either iNOS or eNOS: in normal physiological conditions, BDKRB2 couples through $G_{\alpha q}$/11 and results in calmodulin-dependent activation of eNOS; whereas, in the inflammatory conditions (myocardial infarction, ischemic stroke, acute peripheral arterial occlusion), B1R couples through $G_{\alpha i}$, $G_{\beta\gamma}$ and results in activation of iNOS through the ras-raf-mek-erk-map kinase pathway [14]. Hence, the putative ACEI-BDKRB1-iNOS and ACEI-BDKRB2-eNOS signaling pathways may be of significance as a target for anti-atherogenic and pro-arteriogenic therapies in future.

Indeed, accumulating evidence suggests that BDKRB1 are amplified and expressed constitutively in PBMC subtypes such as macrophages [33]. Our research group demonstrated, that in particular BDKRB1 signaling regulates arteriogenesis by modulation of monocyte/macrophage migration. Moreover, we tested whether bradykinin receptors play a functional role in adaptive arteriogenesis, and analyzed the role of the bradykinin receptor system for collateral artery growth by using a loss-of-function approach. We found a strong reduction in peripheral arteriogenesis for BDKRB1$^{-/-}$ mice and only a minor reduction for BDKRB2$^{-/-}$ mice. A transplantation of wild type into BDKRB1$^{-/-}$ mice recovered the loss of arterial flow after an arterial occlusion surgery, as seen in untreated BDKRB1 mutant mice (gain of function). The enhanced expression of BDKRB1 on immune cells seems to be the pivotal determinant during collateral artery growth and vascular regeneration [4]. Our finding that ACEI treatment might activate BDKRB1 has a clinically perspective and evidence is growing that BDKRB1 can be activated by ACEI directly on the extracellular loop without altering conformational change [12]. Interestingly, our correlation analyses between bradykinin receptor expression and endothelial function shows that there is a positive correlation between FMD and BDKRB1 exclusively in female patients. This is indeed consistent with the findings of Wu et al. [34], who previously speculated here that sex differences in BDKRB1-induced cytokine production may occur in response to ACEI therapy. Indeed, our results here also suggest a possible sex-specific difference in BDKRB1-mediated endothelial function in response to ACEI therapy that needs to be further investigated.

Limitations

The current cross-sectional study is aimed at analyzing the gene expression of bradykinin receptors and ACE in peripheral blood mononuclear cells from patients with ACEI or ARB treatment. Here, we did not conduct any new pharmacological therapy, therefore, the evidence level grade is lower than that of a randomized clinical trial (RCT) or cohort study.

Conclusions

We firstly showed that ACEI treatment enhances total nitrite/nitrate concentration in patients with underlying heterogenous cardiovascular diseases. NO production might also enhance endothelial function in the ACEI treatment group as previously reported, however FMD

measurements showed no differences between the medication treatment groups. The selection of patients with different and concomitant cardiovascular diseases and risk status might influence FMD analysis. FMD is known to be strongly affected by different risk factor such as hypertension, diabetes or severity of atherosclerosis status [25]. Indeed, we demonstrated that FMD is strongly negatively correlated with age in patients with concomitant ischemic vascular disease (CAD, PAD and CVD) and hypertension. Hence, FMD is sensitive to underlying heterogenous cardiovascular diseases, and was again shown to be a strong determinant of vascular aging.

Secondly, ACEI treatment induces the upregulation of BDKRB1, but the downregulation of BDKRB2 mRNA expression in PBMC from patients with cardiovascular disease. The role ACEI-bradykinin receptor signaling pathway is expected to redirect away from pathologic atherosclerosis towards physiological arteriogenesis, which is worthy of further investigation.

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Conflict of interest
The authors have declared no conflict of interest.

Correspondence address
Philipp Hillmeister, PhD
Brandenburg Medical School (MHB)
Faculty of Health Sciences (FGW)
Center for Internal Medicine I.
Department for Angiology & WalkByLab
Campus University Clinic Brandenburg
Hochstrasse 29
14770 Brandenburg an der Havel
Germany

p.hillmeister@klinikum-brandenburg.de

Original communication

The impact of percutaneous peripheral interventions on endothelial function

Christos Rammos, Martin Steinmetz, Mirjam Johnstone, Anna Manzke, Julia Lortz, Olga Petrikhovich, Ulrike Hendgen-Cotta, Rolf A. Jánosi, and Tienush Rassaf

Department of Cardiology and Vascular Medicine, West German Heart and Vascular Center Essen, University of Duisburg-Essen, Germany

Summary: *Background:* Treatment of symptomatic peripheral artery disease (PAD) through endovascular interventions is the primary revascularization strategy. Interventions restore perfusion but may cause severe injury to the vascular endothelium, which regulates vascular tone. Endothelial dysfunction is involved in the progression of cardiovascular disease, with higher incidences of vascular events. We aimed to determine the impact of percutaneous interventions on change in endothelial function. *Patients and methods:* Endothelial function was determined using flow-mediated dilation (FMD) before, the day after lower limb intervention with paclitaxel-coated balloons or stent guided interventions and after a six-month follow-up in the target limb, control limb and the systemic circulation in 42 PAD patients aged 70.2±9 years and 66% men. Additionally, macro- and microvascular function were assessed. *Results:* In PAD patients aged 70.2±9 years and 66% men, we observed an immediate enhancement of macro-, microvascular and endothelial function after endovascular treatment (FMD of superficial femoral artery (SFA) 3.7±0.2% to 4.1±0.1%, n=42, p=0.02), a sustained long-term improvement after 6-months (FMD SFA 3.7±0.2% to 4.2±0.1%, n=42, p=0.01), and moreover an improved systemic endothelial function (FMD brachial artery 4.3±0.1% to 4.7±0.2, n=42, p=0.01) following peripheral interventions. Subgroup analysis however revealed that following paclitaxel-based percutaneous intervention, the paclitaxel dosage applied was inversely related to the chronic improvement in local endothelial function (r=−0.6, n=22, p=0.005) without evidence for systemic effects (r=−0.25, p=0.27). *Conclusions:* We demonstrate an improved local and systemic endothelial function after treatment of atherosclerotic peripheral disease with a distinguished response after endovascular intervention with higher dosage of applied paclitaxel restraining the benefits. Further studies have to determine the optimal interventional strategy with respect to different treatment modalities to maintain vessel functions.

Keywords: Vascular functions, peripheral interventions, endovascular treatment, endothelial dysfunction

Introduction

Cardiovascular disease (CVD) is the leading cause of death [1]. Atherosclerosis is characterized by atheromatous plaques with low-grade, chronic inflammation that lead to altered vascular functions, blood flow restrictions and ultimately tissue ischemia [2]. Macrovascular implications include endothelial dysfunction, which is involved in the initiation and progression of atherosclerosis and is associated to higher incidences of cardiovascular events or the need for interventions [3, 4]. Flow-mediated vasodilation (FMD) is considered the gold standard for determination of endothelial function [5]. FMD was identified as a prognostic relevant surrogate marker in patients with cardiovascular risk factors and established cardiovascular disease [6, 7]. Endothelial dysfunction is associated with major adverse cardio- and cerebrovascular events (MACCE) as heart failure and sudden cardiac death [8].

Atherosclerotic peripheral artery disease (PAD) is a major non-coronary manifestation of CVD. Treatment of symptomatic PAD through endovascular techniques has gained widespread acceptance and is now recommended as the primary revascularization strategy [9]. Percutaneous transluminal angioplasty (PTA) with uncoated balloons has a high initial success rate, while restenosis occurs in the superficial femoral artery in up to 60% [10]. One approach to this challenge has been the development of drug-coated balloons (DCB), which allow local delivery of antiproliferative drugs like paclitaxel to reduce restenosis and improve patency [11]. Recently, studies using paclitaxel in the lower extremity have raised contradictory concerns [12].

While the role of paclitaxel on peripheral vascular function in PAD remains scarce, it is obvious that a stenting strategy with a permanent metallic implants in arteries further deteriorates endothelial function [13]. While restoration of tissue perfusion is achieved, interventional strategies affect endothelial function, perpetuating dysfunctional vascular homeostasis [13]. The influence of endovascular interventions has not been investigated with emphasis on acute and long-term effects on endothelial function.

Thus, the aim of the present study was to determine the impact of the interventional strategy on target lesion and systemic endothelial and vascular function.

Patients and methods

Patients with PAD undergoing nonemergent vascular interventions were eligible for participation if they suffered from moderate to severe intermittent claudication, ischemic rest pain or minor ulcer (Rutherford 2–5, Fontaine II–IV) and ultrasound-assessed stenosis grade from 70% with lesion lengths up to 20 cm involving the aortoiliac or femoropopliteal artery. Further inclusion criteria were age between 40 and 85 years old, vessel diameter of $\geq$3.0 mm to $\leq$6.0 mm and a true-lumen guidewire crossing. Exclusion criteria included pre-existing aneurysm formation, thrombolysis within 72 hours prior to the index procedure, life expectancy less than 12 months, known or suspected active infection and angiographic evidence of thrombus within target vessel. 50 participants provided written informed consent, with 8 lost to follow-up yielding 42 available for analysis. The procedures were in accordance with the Declaration of Helsinki and the institutional Ethics Committee of the local University approved the study protocol (17-7387-BO).

Interventional procedures were conducted in a single-center tertiary referral center. Commercially available DCBs, stents and devices for mechanical debulking and atherectomy were allowed at the physician's discretion. Total paclitaxel dosages, which were applied during the respective interventions were calculated using length, size and paclitaxel density of the dedicated DCBs. Patients were examined at baseline, 2–3 days after peripheral intervention and after a 6-months follow-up.

Blood was drawn at baseline and follow-up for clinical routine and the local University Hospital Institute of Clinical Chemistry and Laboratory Diagnostics performed all analyses unless noted otherwise.

Endothelial function

The primary objective was the systemic and local endothelial function as determined by FMD of the brachial and femoral artery.

Local and systemic endothelial function was determined by noninvasive technique FMD of the brachial or femoral artery as previously described [14–16]. Briefly, with the use of a 12-MHz linear-array transducer and the CX-50 system (Philips Healtcare, Germany), the brachial (BA) and femoral artery diameter were acquired proximal of the antecubital fossa or distal the common femoral artery, respectively, before and immediately at 20, 40, 60, and 80 seconds after cuff deflation of 5-minutes forearm or upper thigh arterial occlusion at 250 mmHg of pressure with a 23–40 wide or 40.6–66 cm wide cuff for the upper arm or thigh, respectively. BA diameter was measured 2–3 cm proximal to the elbow, and proximal SFA was measured 2 to 5 cm distal to femoral bifurcation in a vessel section without visible intima media protrusions. End-diastolic frames were analyzed with an automated analysis system (Brachial Analyzer, Medical Imaging Applications, Iowa City, IO). Nitroglycerin-mediated vasodilation (NMD) i.e., endothelium-independent vasodilation was measured at 4 minutes after 400 µg sublingual nitroglycerin in patients with adequate blood pressure. FMD was determined as the maximal percent diameter change of the arterial diameter measurement relative to the baseline measurement. The measurements were performed at standardized room temperature (about 21 °C) after 15 min of acclimatization. Investigators were blinded in regard to the treatment received.

Macrovascular function

The Ankle-Brachial Index (ABI) serves as a useful tool for diagnosis of PAD and cardiovascular risk and was assessed as described [17]. The measurements were performed at standardized room temperature after 15 min acclimatization.

Microvascular function

Reactive Hyperemia (RH) and the related measure of shear stress are strongly related to cardiovascular risk factors and RH was determined using doppler flow signals recorded before and immediately at 10, 30, 50, 70 and 90 seconds after cuff deflation of thigh arterial occlusion at a pressure 250 mmHg. RH was calculated as the area under the curve subtracted from the preocclusion baseline flow.

Biomarkers of vascular function

Blood was drawn at baseline and at 6 months follow-up for the determination of biomarkers of vascular function and 5 ml was centrifuged at 800 g for 10 min (4 °C). The resulting plasma aliquots were snap frozen in liquid nitrogen and stored at −80 °C until further analysis. Macrophage migration Inhibitory Factor (MIF) and Endothelin 1 (ET-1, Quantikine, R&D Systems, Minneapolis, USA) and Monocyte chemoattractant protein-1 (MCP-1, Human CCL2/MCP Quantikine Immunoassay, R&D Systems, Inc. Minneapolis, MN, USA) levels were measured by quantitative sandwich enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's protocols, as previously described [18].

Furthermore, inflammation markers (CRP, HS-CRP, IL-6) cardiac function (Troponin and NT-proBNP), lipid metabolism (LDL-C and Lp (a)) and endothelial function markers (Cell-free Hb and total Hb) were determined.

Statistics

Results are expressed as mean±standard deviation (SD) unless stated otherwise. Due to explorative design of the study no power calculations are given. All data were checked for normality distribution using Kolmogorov-Smirnov test

Table I. Baseline characteristics

Characteristics	
n	42
Age (y)	70.2±9.9
Men	28 (66%)
BMI (kg/m^2)	27.2±4.5
Rutherford classification	
Rutherford 2–3	31 (74%)
Rutherford 4	4 (9%)
Rutherford 5	7 (17%)
Medication	
Statins	34 (80%)
Aspirin or clopidogrel	38 (90%)
CVRF	
Hyperlipidemia	33 (78%)
Smoking	32 (76%)
Diabetes mellitus	18 (42%)
Hypertension	39 (92%)
Coronary artery disease	30 (72%)
End-stage renal disease	3 (6%)
Prior stroke	13 (30%)
Prior MI	13 (30%)

Data is given as n or mean±SD (%). BMI: Body mass index; CVRF: cardiovascular risk factors; MI: myocardial infarction.

Table II. Procedural characteristics

	n (%)
Aortoiliac lesion	14 (33%)
Femoropopliteal lesion	28 (67%)
Moderate calcification	14 (33%)
Severe calcification	28 (67%)
Chronic total occlusion	22 (52%)
Denovo lesion	31 (74%)
Restenosis	11 (26%)
Radiation dose (µGy/m^2)	5304±10065
Radiation time (min)	18.9±10.9
Contrast agent (ml)	89.2±36.4
Stenosis grade (%)	90.7±11.6
Lesion length (mm)	117±66.1
Vessel diameter (mm)	5.1±1.4
Mechanical debulking (Rotarex S, Straub medical)	9 (21%)
Directional atherectomy (HawkOne, Medtronic)	2 (5%)
Rotational atherectomy (Jetstream, Boston Scientific)	8 (19%)
Interventions with stent	21 (50%)
Total number of stents	28
Average length of stents (mm)	88.74±91.9
Interventions with DCB	22 (52%)
Total number of DCBs	71
Average length of DCBs (mm)	169.3±106.0
Aortoiliac TASC classification	
A	2 (17%)
B	7 (58%)
C	3 (25%)
Femoropopliteal TASC classification	
A	6 (19%)
B	6 (19%)
C	17 (55%)
D	2 (7%)

Data is given as mean±SD; n (%). DCB: drug coated balloon.

and no departures were noted. Paired Student t-test was used for statistical analyses within the groups. Differences between groups were compared using unpaired Student's two-tailed t-test. Correlations between individual parameters were calculated using univariate analyses. Results are expressed as Pearson's r and corresponding p values. P values of less than 0.05 were regarded statistically significant. All statistical tests were conducted using SPSS 21.0 (IBM) and Prism 8.0 (GraphPad).

Results

A total of 50 patients with PAD were included in the study. Of all PAD-patients initially enrolled, 4 were lost to follow up and 4 refrained from further participation yielding n=42 for postinterventional evaluation. All patients underwent a vascular intervention after enrolment, due to symptomatic PAD with Rutherford class 2–3 in 74% (n=31) of cases and Rutherford class 4–5 in 26% (n=11) of cases. Baseline characteristics are given in Table I. Statins were prescribed in 80% (n=34) of patients and antiplatelet therapy in 90% (n=38). Traditional risk factors were hypertension in 92% (n=39), hyperlipidemia in 78% (n=33) and smoking in 76% (n=32) of patients.

We first determined the multilocular endothelial function in PAD and non-PAD controls (electronic supplementary material [ESM] 3). Baseline brachial and femoral endothelial function was reduced in PAD patients as compared to controls (brachial 4.2±0.1 vs. 5.1±1.4, p=0.02; femoral 3.7±0.1 vs. 4.7±0.2, p<0.01). Determination of multilocular endothelial function correlated comparing brachial and femoral FMD in controls (r=0.7; p<0.001; ESM 1A) and in PAD patients with a lesser extent due to atherosclerotic lesions in the lower limb (r=0.4; p<0.001; ESM 1B).

Procedural characteristics are given in Table II. Aortoiliac lesions were treated in 33% (n=14) and femoropopliteal lesions in 67% (n=28). Chronic total occlusions were treated in 52%, and average lesion length was 117±66 mm. Debulking (Rotarex S, Straub medical) was performed in 21%, rotational atherectomy (Jetstream XC, Boston Scientific) in 19% and directional atherectomy (HawkOne, Medtronic) in 5%. Bail-out stenting (Dynamic and Pulsar, Biotronik; BioMimics, Veryan and Everflex, Medtronic) was necessary in 50%, when dissections were obvious. Overall DCB rate was high with n=22 using dedicated devices (Passeo Lux, Biotronik).

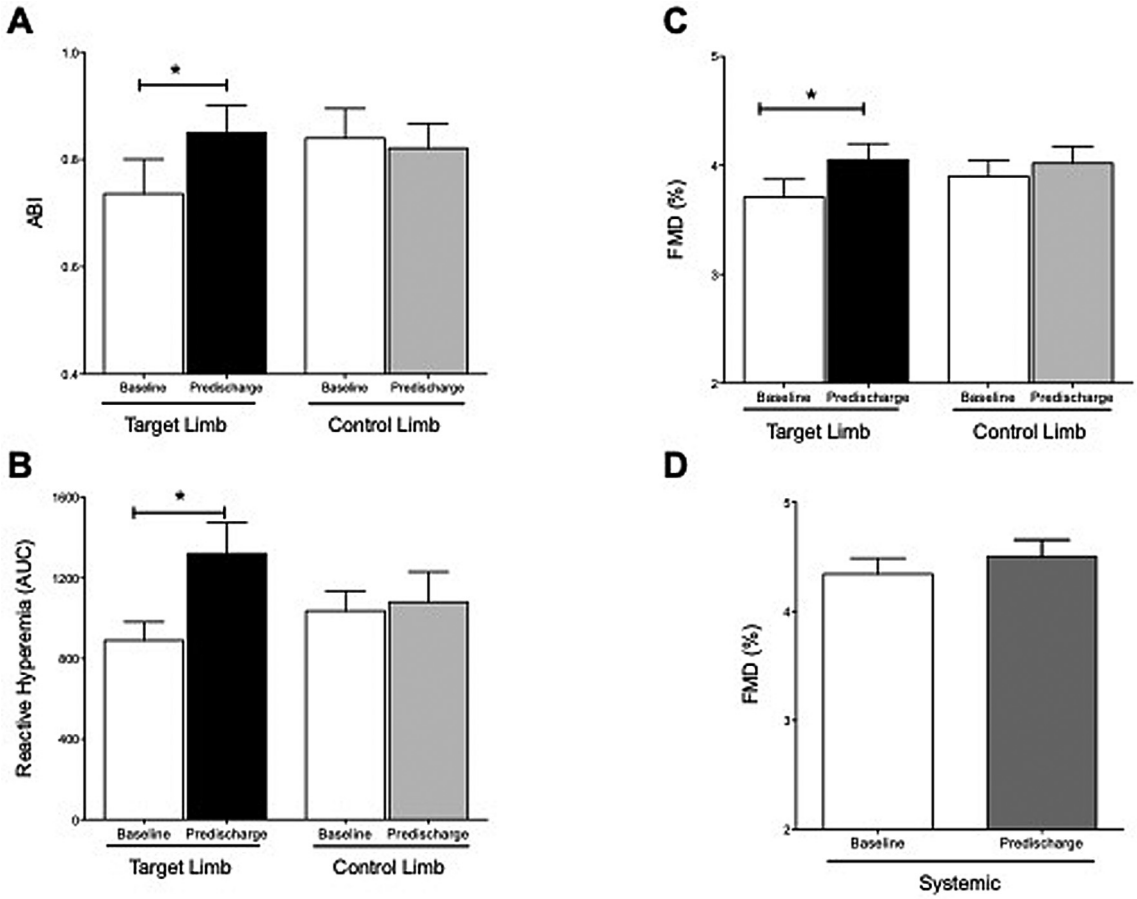

Figure 1. Immediate impact of endovascular treatment on macro-, microvascular and endothelial function in PAD patients. (A) Higher ankle-brachial index (ABI) – indicating superior macrovascular function- is observed after endovascular treatment; (B) Significant increase in reactive hyperemic flow as a result of improved microcirculation in the treated limb; (C) Postinterventional improvement of local endothelial functions is observed only in the target limb and not in the control limb; (D) systemic endothelial response remain unaffected. FMD: flow-mediated dilation. *p<0.05.

Acute improvement in target limb endothelial function

The immediate impact of endovascular treatment on the arterial tree was determined through characterization of macro-, microvascular and endothelial function. After endovascular treatment, a higher ABI was shown in the treated extremity indicating superior macrovascular function (0.74±0.1 to 0.85±0.1, p=0.04; Figure 1A). This was corroborated by an increase in reactive hyperemia as well as in an augmentation in target limb endothelial function (RH 890±92 to 1322±155, p=0.02; FMD 3.7±0.2% to 4.1±0.1%, p=0.02; Figures 1B–1C). Notably, immediately after vascular interventions no effect was observed in the control limb regarding macro-, microvascular or local endothelial function or systemic endothelium (p>0.05 for all comparisons, Figures 1A–1D).

Chronic improvement in local and systemic endothelial function

After the six-months follow-up, a persistent augmentation in macro and microvascular function was observed as determined by ABI and RH in the target limb, while the control limb remained unaffected (ABI 0.9±0.1, p=0.009; RH 1201±150, p=0.046; both compared to baseline; control p>0.05; Figures 2A–2B). A sustained improvement of endothelial function was observed in the target limb and moreover in the control limb and furthermore in the systemic circulation after endovascular treatment (FMD target 3.7±0.2% to 4.2±0.1%, p=0.01; FMD control 3.9±0.1% to 4.3±0.2%, p=0.02; FMD brachial 4.3±0.1% to 4.7±0.2 p=0.01; Figures 2C–2D). No impact was seen for markers of vascular functions (MIF, ET-1, MCP-1, Lpa, cell-free Hb or hs-CRP) while a reduction was observed only for LDL-C (ESM 4).

Further subgroup analysis aimed to differentiate location and treatment methods used. An improved endothelial function following endovascular treatment in the femoro-popliteal segment was determined as compared to the aortoiliac segment (FMD femoropopliteal 3.6±0.2% to 4.1±0.1%, p=0.01; FMD aortoiliac 4.1±0.3% to 4.4±0.2%, p=0.76). The improved endothelial function after 6-months was moreover detected using a stentless approach as compared to a stent-guided intervention (FMD stentless 3.4±0.2% to 3.9±0.2%, p=0.03; FMD stent-guided 4.15±0.2% to 4.5±0.2% p=0.3).

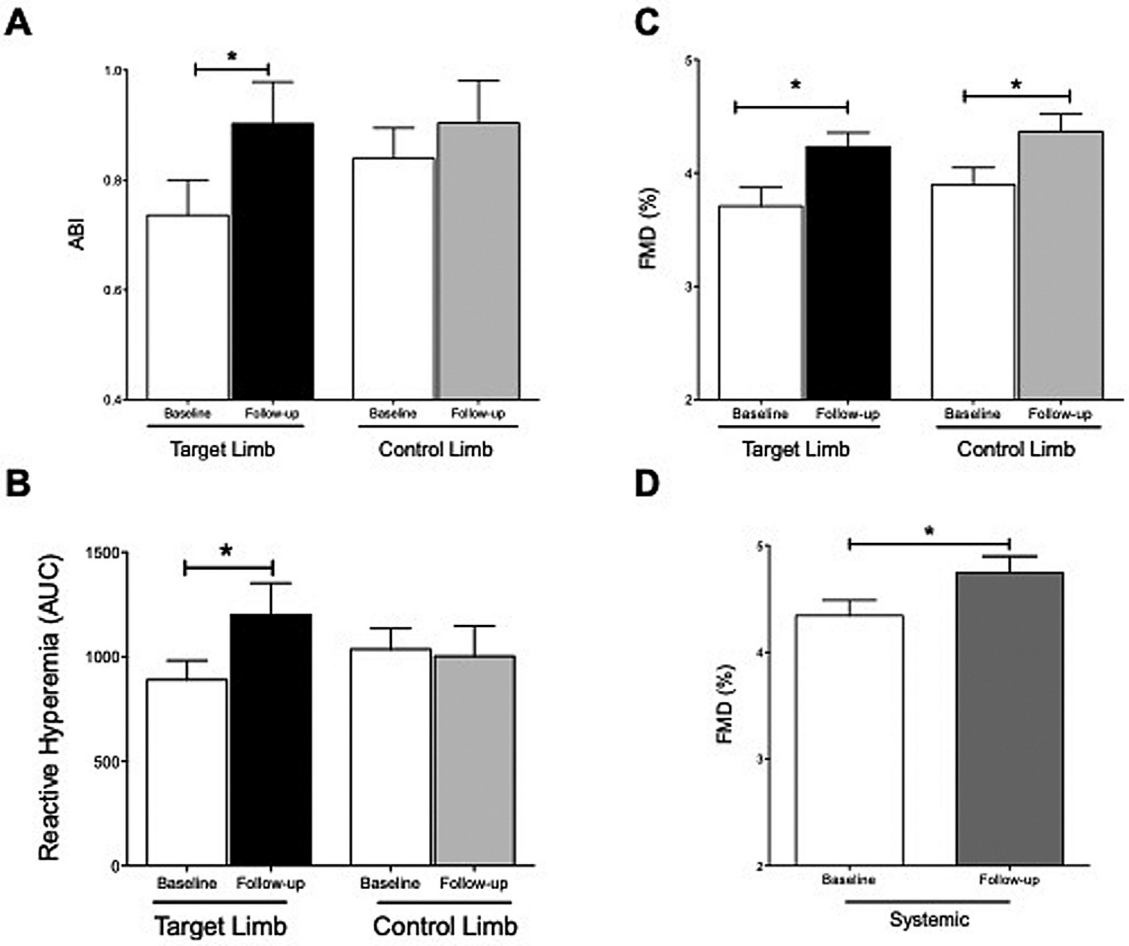

Figure 2. Long-term effect on macro-, microvascular and endothelial function in PAD patients after endovascular treatment. (A) Improved ankle-brachial index (ABI) after endovascular treatment implies persistent augmentation in macrovascular perfusion; (B) Sustained increase in reactive hyperemia suggests chronically improved microcirculation in the treated extremities while controls remain unaffected; (C) Sustained improvement of endothelial function is observed in the target limb and moreover in the control limb; (D) The prognostic relevant systemic endothelial response is markedly enhanced after endovascular treatment. FMD: flow-mediated dilation. *p<0.05.

Impact of paclitaxel on the endothelium

We further sought to investigate the impact of paclitaxel-coated balloons on local endothelial function. For this subgroup analysis, only lower limb interventions with dedicated DCBs were included (n=22). Corroborating our results, in the DCB subgroup an overall improvement of local endothelial function was detected after 6 months of follow-up as compared to baseline (FMD 3.4%±0.2% to 4.2%±0.1%, p=0.007; Figure 3A).

Calculations of total paclitaxel dosages, which have been applied during the respective interventions using length and size of the dedicated DCBs (with 3µg/mm^2 drug), revealed a different picture. An inverse relation was observed for paclitaxel dose and improvement in endothelial function, showing a negative impact of paclitaxel on the endothelium through drug application (r=−0.6, p=0.005; Figure 3B). Of note, baseline and procedural characteristics were balanced between the improved and reduced endothelial-response group (CTOs, lesion length, bail-out stent rate, NMD, ESM 5 and 6). We then investigated the impact of peripheral paclitaxel application on systemic vascular functions. In the brachial artery FMD measurement, no relationship of paclitaxel application after peripheral interventions was observed (ESM 2).

Discussion

We provide conclusive evidence for the impact of endovascular treatment on vascular function. Our findings are threefold: 1) we provide evidence for augmented local macro-, microvascular and endothelial function acutely after endovascular treatment; 2) We show that the improved vascular function is sustained after a 6-months follow up, with an additional improvement of systemic endothelial functions; 3) Our findings provide first proof that endovascular treatment in PAD patients using dedicated DCB affects local endothelial function. Intriguingly, we identify the dosage of paclitaxel based on vessel size and DCB-treated lesion length as a restrictor of potential improvements in endothelial function.

A healthy endothelium exerts important functions, regulating vascular tone and structure, inhibition of platelet and leukocyte adhesion as well as maintaining a balance of

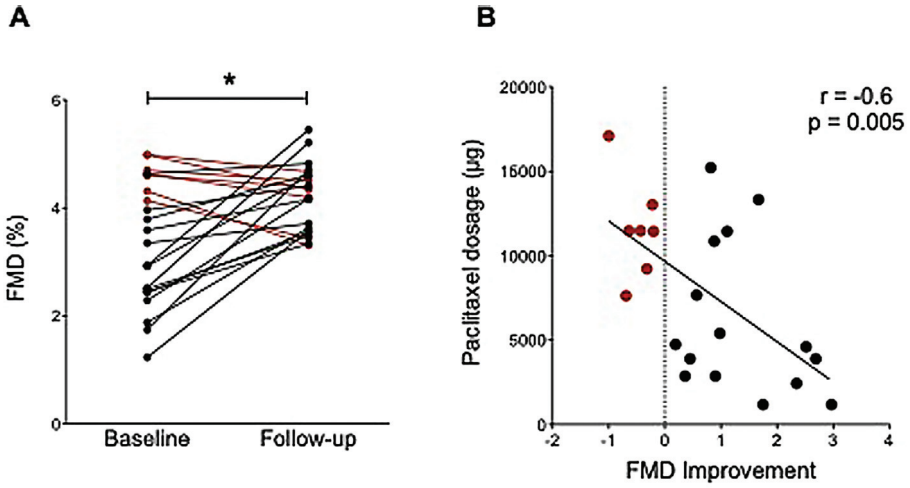

Figure 3. Effect on local endothelial function 6 months after percutaneous intervention and relation to paclitaxel dosage. (A) Postinterventional improvement of local endothelial functions is observed in the target limb as compared to baseline after endovascular treatment (FMD, flow-mediated dilation p=0.007); (B) The paclitaxel dosage applied through drug coated balloons inversely affects chronic improvement in endothelial functions (decreased endothelial-response in red dots, black dots indicate improved endothelial-response; r=−0.6, p=0.005).

antioxidant, profibrinolytic and prothrombotic activity. Until now, the brachial artery endothelial function measured by FMD is known to be predictive for cardiovascular events and FMD is considered the most reliable tool to determine nitric-oxide mediated vasodilation [19]. Event prediction is evident for people free of CVD, with traditional risk-factors or established coronary artery disease [6, 20].

We now show that brachial and femoral artery endothelial function correlate in non-PAD controls and PAD subjects. Of note, in PAD patients a reduced response to reactive hyperemia was observed in the femoral artery. Mechanistically this is thought to be due to evident atherosclerosis with vascular calcification and potential media sclerosis. Our findings are corroborated by studies showing that SFA FMD is nitric oxide mediated and diminished in PAD as compared to healthy volunteers [21, 22]. This is of broader interest for studies investigating interventional strategies due to the easily accessible arterial structures for in-depth characterization of vascular functions.

Based on our findings we characterized the acute impact of endovascular interventions on vessel functions. For the coronary bed, data was gathered showing a reduction of endothelial function after bare-metal stenting [13]. These findings were additionally supported by endothelial dysfunction after different next-generation drug-eluting coronary stents [23]. Recent work raised controversial findings regarding vasomotion–responses after drug-eluting and bioabsorbable stent treatment in coronary arteries [24]. Clearly, the mechanisms behind these findings are incompletely understood and may include endothelial denudation and delayed re-endothelialization, amongst others [25].

Based on our model of PAD we are now able to show that peripheral interventions impact on local and on systemic vascular functions. This was shown in a holistic approach determining macrovascular, microvascular and endothelial functions. Impressively, we found improved vascular functions immediately after the interventional procedure and moreover a sustained effect during the 6-months follow-up in the target vessel. This effect was more pronounced in the femoropopliteal segment and with a stentless approach. Mechanistically, stent implantation and angioplasty is believed to cause denudation of the endothelium and deprivation of vasomotor functions through rigid stent systems to prevent relaxation and constriction of the artery [26]. Moreover, stents are considered natural barriers for the endothelial repair processes due to altered shear stress and thus impaired endothelial function [25].

The detailed mechanism of the interventional method chosen has thus to be considered when investigating vascular functions. We used various treatment strategies including angioplasty, stenting, atherectomy and debulking techniques. Standard angioplasty and stents do not remove the atheroma but press or crush it and redistribute it in and along the arterial wall. Thus, vessel compliance is supposed to be further reduced with these techniques [22]. Atherectomy and debulking do however remove atherosclerotic lesions allowing a minimal consequent vessel barotrauma within postdilation, increased luminal gain, and consecutively improved vessel compliance [27]. Due to small numbers treated with debulking and atherectomy in this study it is suggestive that novel techniques might lead to an improved vessel function through the reduction of atherosclerotic burden. Clearly, further trials are needed to gain insight for this important issue.

The impressive effect of paclitaxel on the vascular endothelium points to the recent debate concerning adverse events after DCB treatment [12, 28]. Of note, we did not observe an impact of paclitaxel on systemic endothelial functions. Thus, based on the small sample size in our study, we would exclude a systemic effect of paclitaxel administration on remote endothelium. However, larger studies have to enlighten this important issue, as differentiated information is missing regarding nicotine

abuse, changes in statin therapy or other factors influencing endothelial function. Our data however, support the concept of dosage-dependent relationship with decreased endothelial function in the treated limb [29]. Our findings are corroborated by preclinical studies that show a marked impairment in vasocontractile functions after paclitaxel administration *exvivo* [30].

Remarkably, we clearly show an effect on the systemic endothelial response after a local treatment of the peripheral arteries. It would be tempting to speculate that through peripheral interventions a reduction of symptoms with enhanced peripheral blood flow and improved vasodilation capabilities occurs, that could finally translate to an improved overall mortality benefit. However, despite the strong biological effect, we could not show an additional impact on biochemical markers.

Limitations

Due to the explorative approach, we performed a monocentric non-randomized study. Finally, more studies have to be performed with subgroup analysis and special emphasis on underlying target lesion location and characteristics and potential improvement of vascular functions. Furthermore, a selected cohort with strict inclusion and exclusion criteria of a singular manifestation of PAD in the SFA would potentially yield stronger outcome, while this was not the scope of the present work. Finally, our findings regarding improved endothelial function of the femoral artery have still to be proven predictive for overall vascular events.

Conclusions

Evidence is provided for an improved local endothelial function after treatment of atherosclerotic peripheral vascular disease. This improvement is sustained after a chronic follow up, with an additional improvement of the systemic endothelial function. The usage of paclitaxel coated DCBs seem to abrogate the benefits of endovascular treatment on endothelial function. Further studies are necessary to determine the optimal interventional strategy with respect to different treatment modalities to maintain vessel functions and to show an overall cardiovascular prognostic impact.

Electronic supplementary material

The electronic supplementary material (ESM) is available with the online version of the article at https://doi.org/10.1024/0301-1526/a000901

ESM 1. Multilocular determination of endothelial function. Determination of endothelial function by flow-mediated dilation (FMD) of the brachial and femoral artery correlates in control subjects (A) and subjects with PAD (B) (Figure)

ESM 2. Relation of systemic endothelial function 6 months after percutaneous intervention and relation to paclitaxel dosage. The paclitaxel dosage applied through drug-coated balloons does not affect chronic improvement in endothelial function in the brachial artery (Figure)

ESM 3. Baseline characteristics of non-PAD controls (Table)

ESM 4. Lipid profile, markers of vascular function and inflammation (Table)

ESM 5. Baseline and procedural characteristics (Table)

ESM 6. Components of flow-mediated vasodilation (Table)

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ORCID
Christos Rammos
https://orcid.org/0000-0003-3468-9945

Correspondence address
Christos Rammos, MD, FESC
West German Heart and Vascular Center Essen
Department of Cardiology and Vascular Medicine
University Hospital Essen
Hufelandstraße 55
45147 Essen
Germany

christos.rammos@uk-essen.de

Original communication

Factors predicting long-term outcomes of percutaneous angioplasty and stenting of the superior mesenteric artery for chronic mesenteric ischemia

Joris Awouters[1], Thomas Jardinet[1], Martin Hiele[2], Annouschka Laenen[3], Steven Dymarkowski[1], Inge Fourneau[4], and Geert Maleux[1]

[1] Department of Radiology, University Hospitals Leuven, Belgium
[2] Department of Gastroenterology and Hepatology, University Hospitals Leuven, Belgium
[3] Interuniversity Institute for Biostatistics and statistical Bioinformatics (L-BioStat), Leuven, Belgium
[4] Department of Vascular Surgery, University Hospitals Leuven, Belgium

Summary: *Background:* To analyse the long-term outcomes of percutaneous angioplasty and stenting of the superior mesenteric artery (SMA) in the treatment of chronic mesenteric ischemia (CMI), and to assess predictive factors for a better clinical outcome. *Patients and methods:* Retrospective analysis of 76 consecutive patients, treated percutaneously for CMI between January 1999 and January 2018 and followed up until the end of 2018. Patients' pre-, peri- and post-interventional clinical and radiological data were gathered from the institutional electronic medical records. The Kaplan Meier method with log rank test or the Cox model were used to analyse overall survival; the cumulative incidence function with Pepe and Mori test or the Fine and Grey model were used to analyse relapse-free survival, considering death as a competing event. *Results:* Seventy-six consecutive patients with a mean age of 72 years were included in the study. Catheter-angiography revealed an ostial or non-ostial >90% stenosis in n=23 (29.7%) and n=53 (69.7%) of included patients, respectively. Immediate clinical success was achieved in n=68 (89.5%), and procedural complications were observed in n=13 (17.1%) patients. Long-term follow-up revealed relapse of symptoms in n=21 (28.8%) patients, and overall survival estimates are 81.8%, 57.0% and 28.2% after two, five and ten years of follow-up, respectively. A trend towards longer relapse-free survival was found in the circumferential stenosis group (78.2% at five years) compared with the non-circumferential stenosis group (55.5%) (P=0.063). *Conclusions:* Angioplasty and stenting of the SMA for CMI is relatively safe and effective despite a substantial number of patients experiencing clinical relapse over time. Patients with focal, circumferential stenosis might have longer relapse-free survival than patients with non-circumferential stenosis.

Keywords: Angor, chronic, ischemia, mesenteric, interventional, angioplasty

Introduction

Chronic mesenteric ischemia (CMI) is a rare clinical entity with symptoms including postprandial abdominal pain, weight loss and intermittent diarrhoea. CMI typically occurs in the elderly population, with a predilection for women, and is the result of inadequate blood flow to the intestines, most often caused by progressive, atherosclerotic disease of one or more mesenteric arteries [1]. Treatment of symptomatic CMI is mandatory to prevent acute mesenteric ischemia, which could potentially cause extensive bowel infarction and death. Today, catheter-directed angioplasty and stenting is considered in many centres to be the primary treatment option for CMI owing to the high technical success rate, low complication rate and acceptable short and medium-term clinical follow-up results [2, 3, 4, 5, 6, 7, 8, 9, 10]. In contrast to the percutaneous approach, surgical repair is associated with relatively high perioperative morbidity (15%–33%) and mortality (0%–17%) [11, 12, 13, 14]. Conversely, percutaneous angioplasty and stenting is associated with a high restenosis rate of up to 50% for the SMA and up to 80% of the coeliac trunk [2, 4, 15]. Occlusive disease of the superior mesenteric artery rather than the coeliac trunk seems to be associated with symptoms of CMI [16]. In addition, long-term outcomes [17, 18], as well as factors predictive for better or worse outcomes, are not well understood.

This retrospective study involved an assessment of the short and long-term clinical outcomes of a cohort of

76 patients treated with SMA angioplasty and stenting for symptomatic CMI, related to atherosclerotic stenosis, at a university centre for vascular disease. Factors predicting better clinical outcomes were also analysed.

Patients and methods

Study design

This is a retrospective review of a cohort of consecutive patients treated for symptomatic CMI related to atherosclerotic SMA-stenosis and drawn from the interventional radiology database at a university medical centre for vascular diseases between January 1999 and January 2018. Patients with thrombo-embolic occlusive disease of total atherosclerotic SMA-occlusions were excluded in this study analysis. The study was approved by the local Ethics Committee.

Clinical and radiological data analysis

Demographic data, including symptoms at presentation, comorbidities and preinterventional imaging, were collected from the institution's electronic medical records and the Picture Archiving and Communication System (PACS, Agfa Gevaert, Mortsel, Belgium), respectively. Preinterventional imaging analysis, including the location of the stenosis, degree of stenosis and analysis of circumferential versus focal, non-circumferential aspect of the stenosis, was performed in collaboration consensus by two radiologists (with two and 20 years' experience, respectively).

Preinterventional imaging

Diagnostic preinterventional imaging was performed using of catheter-directed angiography, magnetic resonance (MR) angiography and computed tomography (CT) angiography. Briefly, diagnostic catheter-directed angiography included anteroposterior and lateral flush aortography using a 4 or 5 French (F) pigtail catheter; the volume of nonionic iodised contrast medium iopromide (Ultravist 240, Bayer AG, Berlin, Germany) was 30 ml and the injection rate 10 ml/second.

Three-dimensional MR angiography was performed on a 1.5 T MRI scanner using a six-element sensitivity encoding body coil. Imaging was performed in breath-hold using a coronal 3D centric reordered gradient echo acquisition (TR, 3.36 ms; TE, 1.23 ms; flip angle 25°; slice thickness 0.8 mm; field of view (FOV) 320×350 mm; matrix 336×384; parallel imaging factor 2). Data were reconstructed to an isotropic voxel size of 0.8×0.8×0.8 mm using zero-filling interpolation. Images were acquired during a first pass bolus of gadoterate meglumine at 2 ml/sec, using a standard dose of 0.2 mL/kg (0.1 mmol/kg) body weight.

CT angiography was performed on 4, 16 or 64-row scanners depending on the time period for which the patients were treated; two scan phases were performed: first without contrast medium, mainly to visualise the degree of calcified plaques, followed by an arterial phase using automated triggering in the abdominal aorta at 120 Hounsfield Units (HU). Axial and reconstructed coronal and sagittal images of the arterial phase were performed.

A circumferential stenosis of the SMA was defined as a stenotic plaque invading more than half of the circumference of the SMA vessel wall; whereas a focal stenosis was considered a focal plaque invading equal or less than half of the circumference of the SMA vessel wall.

SMA stenting technique

Patients gave informed consent before the start of the procedure. Under local anaesthesia, percutaneous access was made to the right common femoral or left brachial artery. Using a 5 French pigtail catheter, an anteroposterior and lateral flush aortography injection was performed using a non-ionic iodised contrast medium, or carbon dioxide (CO2) in the event of contraindications for an iodised contrast medium, in order to visualise and confirm the proximal high-grade stenosis of the SMA. Following the intra-arterial injection of 5,000 international units (IU) of heparin, cannulation of the stenosed SMA was carried out using different types of diagnostic 4 or 5 F catheters, including a Simmons 1, Cobra and vertebral catheter (Terumo Europe, Leuven, Belgium; Cook Medical, Bloomington, IN, USA). After exchange for a coronary 0.014 inch guide wire (Stabilizer, Cordis, Roden, the Netherlands) and a 6F guiding catheter (Viking, Guidant Vascular, Santa Clara, CA, USA) or guiding sheath (Flexor, Medical, Bloomington, IN, USA), the SMA stenosis was predilated with a 5 or 6 mm diameter and 20 mm long rapid exchange angioplasty balloon catheter. Finally, different types of vascular stents, including Hippocampus renal (Medtronic, Minneapolis, MN, USA), Tsunami peripheral (Terumo Europe, Leuven, Belgium), Corinthian and Genesis (Cordis, Roden, the Netherlands), Herculink and Acculink (Guidant Vascular, Santa Clara, CA, USA), Optimed Sinusstent (Optimed, Ettlingen, Germany), Express Vascular (Boston Scientific, Natick, MA, USA) and two types of coronary stents, namely Coroflex (B.Braun, Melsungen, Germany) and Rebel (Boston Scientific, Natick, MA, USA), were used at the discretion of the attending interventional radiologist. Self-expandable stents were used in case of long (>20 mm length) postostial SMA-stenosis. Postinterventional medical treatment included aspirin 80 mg lifelong and clopidogrel 75 mg for 1 month.

The type of stent used were mainly rapid-exchange 0.014 inch platform balloon-expandable stents dedicated for visceral artery stenting, including Herculink (...); in n=1 an 0.035 inch over-the-wire platform balloon-expanbable stent (Acculink) and in n=1 an 0.035 inch over-the-wire self-expanding stent (Sinusstent) were used related to the unavailability of large diameter (7 mm diameter) rapid-exchange 0.014 balloon-expandable stents at that time. In the remaining 2 patients a coronary stent, Coroflex (n=1) and Rebel (n=1) was used related to the small diameter (4 mm diameter) of the treated vessel segment.

Follow-up

Patients' clinical follow-up was performed by review of the electronic medical records, including all types of follow-up imaging, up to the most recent hospital visit and phone calls with the patient's general practitioner.

Definitions and statistical analysis

Technical success was defined as a residual stenosis <30% as measured on completion of the profile view angiography. Pressure measurements above and below the stenosis were not systematically performed. A technical failure was defined as inability to cross or dilate the stenotic lesion or a residual stenosis >30%. Perioperative complication was defined as an unintended event related to the endovascular procedure and was categorised according to the Society of Interventional Radiology (SIR) classification of procedural complications [19].

Short-term clinical success was defined as a cessation of the clinical symptoms of CMI which prompted the intervention. Long-term clinical success was defined as an absence or significant reduction of the symptoms of CMI up to the end of the follow-up period.

Statistical analysis included estimating symptom relapse rates using the Cumulative Incidence Function (CIF). The Pepe and Mori test was used to assess group differences. The Fine and Grey model was used to assess predictor effects. The Kaplan-Meier method was used for estimating overall survival. The log-rank test was used to compare groups on survival curves. Lastly, the Cox model was used to analyse the effect of stent diameter on survival. Analyses were performed using SAS software (version 9.4 of the SAS System for Windows, Cary, NY, USA).

Results

Patient demographics

The patient cohort comprised 76 patients (39 female) with a mean age of 72 years (standard deviation: 11.1 years; range 35–96 years). Patients' medical comorbidities are summarised in electronic supplementary material (ESM) 1. Fifty of the 76 patients (66%) presented with three or more of the analysed comorbidities. Clinical symptoms at presentation included: postprandial pain (n=51; 67%), weight loss of more than 5 kg over 2 months (n=43; 56.6%), nausea (n=7; 9.2%), vomiting (n=8; 10.5%) and diarrhoea (n=23; 30.3%).

Preinterventional imaging

Non-invasive imaging prior to the intervention included duplex ultrasound (n=5; 6.6%), CT angiography (n=53; 69.7%), MR angiography (n=13; 17.1%). The type of non-invasive preinterventional imaging changed over time as summarised in ESM 2. Procedural angiography revealed ostial SMA-stenosis (n=23; 30.2%) or non-ostial SMA-stenosis (n=53; 69.7%). Fifty CT angiographic studies and four MR angiographic studies included sufficient imaging data for further stenosis characterisation into circumferential and focal stenosis. Circumferential stenosis was identified in 29 patients (53.7%) (Figure 1); in the remaining 25 patients (46.3%), the stenotic plaque was considered as focal and, non-circumferential (Figure 2).

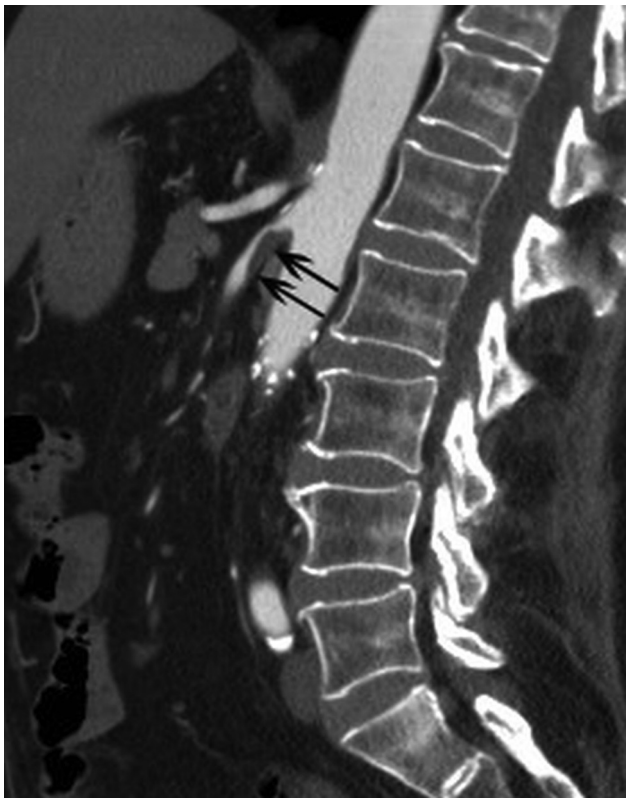

Figure 1. Reconstructed coronal CT-image in a 73-year-old man with clinical symptoms of angor abdominalis demonstrates a non-circumferential, eccentric, high-grade postostial stenosis (black arrows) of the superior mesenteric artery.

Technical and immediate clinical outcome

Vascular access was obtained through the right common femoral artery (n=66; 86.8%) or left brachial artery (n=10; 13.1%). In one patient (1.3%) cannulation of the high-grade stenosis failed resulting in an intention-to-treat immediate technical success rate of 98.7%. The types of stents used were mainly rapid-exchange 0.014 inch platform balloon-expandable stents dedicated for visceral artery stenting, including Herculink (n=8), Tsunami (n=30), Express Vascular (n=8), Corynthian/Genesis (n=6), Hippocampus (n=8); in n=1 an 0.035 inch over-the-wire platform balloon-expandable stent (Acculink) and in n=1 an 0.035 inch over-the-wire self-expanding stent (Sinusstent) were used related to the unavailability of large diameter (7 mm diameter) rapid-exchange 0.014 balloon-expandable stents at that time. In the remaining 2 patients a coronary stent, Coroflex (n=1) and Rebel

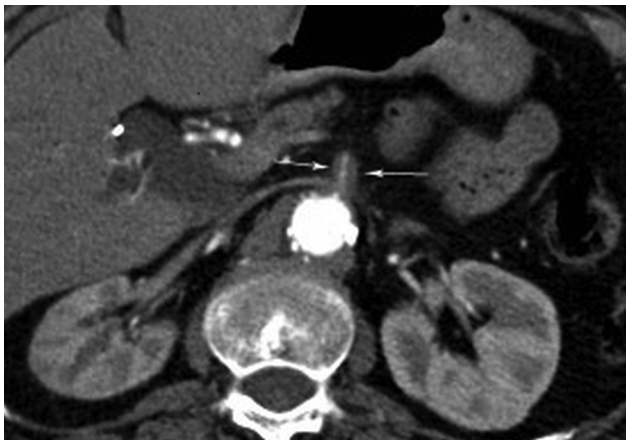

Figure 2. Axial CT-image in an 83-year-old female patient with angor abdominalis shows a circumferential (white arrows) proximal, high-grade stenosis of the superior mesenteric artery.

(n=1) was used related to the small diameter (4 mm diameter) of the treated vessel segment. In 54 patients (71%) one stent was inserted; eight patients (10.5%) received two stents; two patients (2.6%) received three stents; and one patient (1.3%) received 5 stents. The average diameter and length of the stents used was 5.7 mm (4–7 mm) and 17.6 mm (12–40 mm), respectively. After angioplasty and stent placement, the residual stenosis was <30% in all patients.

In addition to the stenting of the SMA, a balloon angioplasty of the coeliac trunk (n=1), stenting of the common or external iliac artery (n=3) and stenting of a renal artery (n=1) was performed in the same session.

In total, 13 patients (17.1%) experienced procedural or immediate postprocedural complications related to the procedure, with major complications in three patients (4%), as summarised in ESM 3. In three cases a pseudo-aneurysm at the access site was managed using an ultrasound-guided thrombin injection; prolonged bleeding at the access site was resolved with 24 hours of external compression. Periprocedural stent dislodgement into the abdominal aorta was managed with retrieval of the stent into the right external iliac artery and postdilatation of the stent in the external iliac artery. The other minor complications, including contrast-induced nephropathy, post-procedural hypotension and retroperitoneal haematoma, were resolved using conservative measures. The major complications included femoral artery thrombosis with non-viable leg ischemia related to the insertion of a closure device (Angioseal, Terumo Europe, Leuven, Belgium) and thrombosis of an aortofemoral bypass graft, both requiring immediate open surgical intervention. Finally, a dissection of the proximal common femoral artery was managed through placement of a stent.

Immediate clinical success was achieved in 68 out of 76 patients (89.5%); in the remaining eight patients, including one patient where there was a failure to cannulate the stenosis, symptom relief was insufficient; 30-day mortality was 2.6%: one patient died due to myocardial infarction 23 days after the index procedure, while another patient died from intestinal ischemia 22 days after the stent procedure. In the latter patient, a Herculink stent 6 mm/18 mm was inserted, and patient's risk factors included dilated cardiomyopathy, peripheral vascular disease and renal insufficiency. Follow-up imaging was not available for either of these two patients.

Long-term outcome

In ten patients (13.2%), a reintervention was performed to manage an in-stent-occlusion (n=2), an in-stent >90% restenosis (n=3) or an in-stent >70% restenosis (n=5) after a mean time of 26.5 months. Reinterventions included re-stenting (n=7) and open surgical bypass (n=3), resulting in cessation of symptoms in seven of the ten patients. Two patients underwent a third endovascular intervention to treat a recurrent in-stent restenosis.

The mean clinical follow-up period was 45.5 months; three patients were lost to follow-up. 21 patients (28.8%) presented with relapse of symptoms during follow-up. Average time to symptomatic relapse was 14.9 months. Cumulative Incidence Function estimates a relapse-free number of patients of 78.9%, 72.3% and 70.3% after two, five and ten years of follow-up, respectively (Figure 3). Ten out of 21 patients with persistent or recurrent symptoms of chronic mesenteric ischemia were re-treated as described supra; the remaining 11 patients did not receive additional interventional or surgical treatment: repeat imaging did not demonstrate SMA-stenosis (n=8), occlusion of the SMA distal tot the stented segment without potential for surgical revascularization (n=1), severe comorbid disease, including stroke, and early death (n=2).

At the end of the follow-up period, 45 patients (59.2%) had died, with a median overall survival of 79 months. Cause of death was determined in 35 patients and is summarised in ESM 4. Another 2 patients died related to intestinal ischemia; however, no imaging nor autopsy was available to determine if the SMA-stents were patent or not in these cases. Kaplan-Meier estimates for overall survival were 81.8%, 57.0% and 28.2% at two, five and ten years of follow-up, respectively (Figure 4). Demographic and angiographic factors potentially predicting risk for early or late restenosis are summarized in ESM 5.

Patient freedom from symptom relapse was compared in the group of patients with a circumferential stenosis of the SMA versus patients with a focal, non-circumferential stenosis, and showed a trend towards longer relapse-free survival in the circumferential stenosis group (78.2% versus 55.5% at five years); however, the difference was not statistically significant (P=0.063) (Figure 5); survival analysis between both groups was unable to demonstrate any statistically significant difference (P=0.64) (Figure 6). Other factors also showed no difference in relapse-free survival, including patients presenting with an ostial versus non-ostial stenosis (P=0.35) and patients treated with smaller or larger stent diameters (P=0.33).

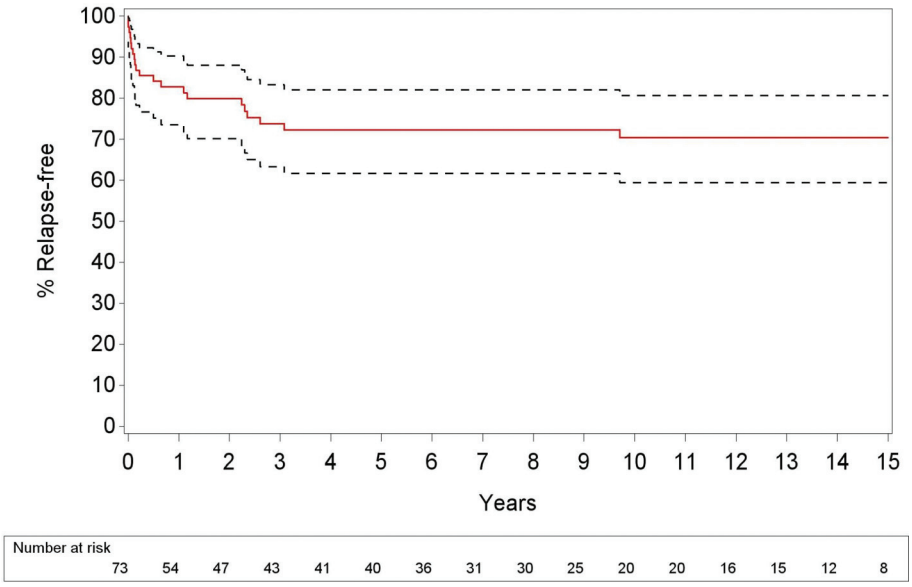

Figure 3. Cumulative incidence function estimates a relapse free number of patients after superior mesenteric artery stenting of 78.9%, 72.3% and 70.3% after respectively 2, 5 and 10 years of follow-up.

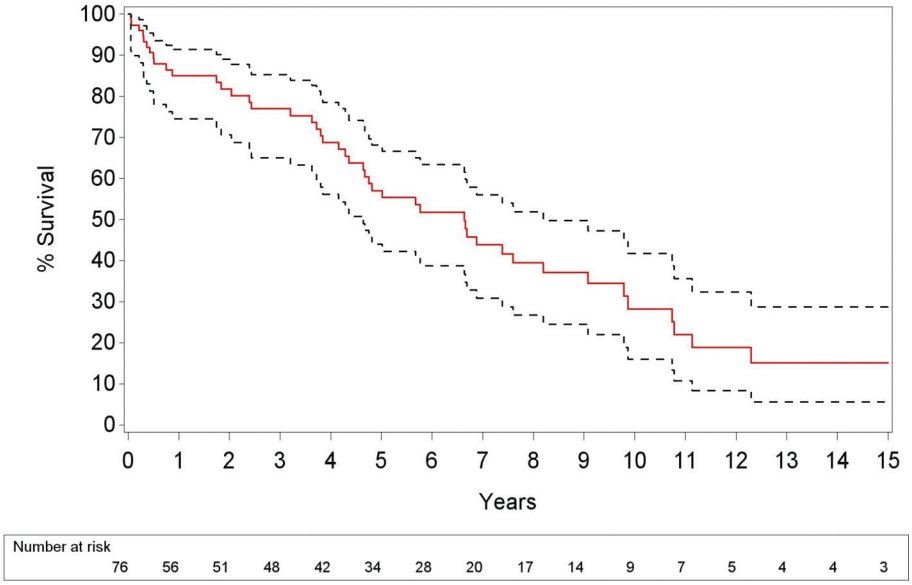

Figure 4. Kaplan-Meier estimates for overall survival after superior mesenteric artery stenting was 81.8%, 57.0% and 28.2% at respectively 2, 5 and 10 years of follow-up.

Discussion

Recent, high-volume studies show that the technical success rate of catheter-directed percutaneous angioplasty and stenting for symptomatic SMA stenosis is very high, ranging between 90% and 100%, as summarised in ESM 6. Additionally, SMA angioplasty and stenting is considered to be a safe procedure with a complication rate mostly below 15%. The total complication rate in the presented study was 17%; major complications (SIR classification C-F) were observed in three patients (4%) and consisted in access-related complications, successfully managed with open or endovascular repair. These high success rates associated with a low rate of serious procedural complications have resulted in the endovascular approach to manage symptomatic SMA-stenoses being the first-choice treatment in many institutions, with surgical repair as a back-up in the event of endovascular failure [13, 14, 20]. The major drawback of the endovascular approach is the relatively high recurrence rate of in-stent restenosis, ranging between 30% and 45%; in addition, further progression of the atherosclerotic disease over the whole visceral vascular bed might even increase these numbers. In the presented study, 13% of patients underwent a redo endovascular or surgical procedure to manage in-stent occlusive disease. Although redo procedures with or without stenting can be performed, resulting in a primary-assisted patency rate of more than 90% [18], late death related to intestinal ischemia was 8.6% in this study. In order to lower the recurrence rate of intestinal ischemia

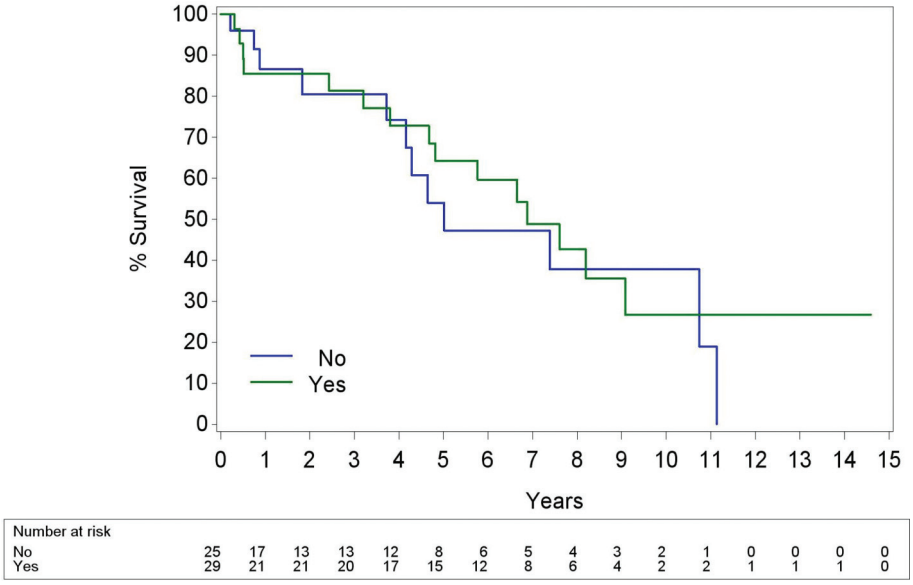

Figure 5. Cumulative incidence function estimates a trend towards longer relapse free survival in the circumferential stenosis group (78.2% versus 55.5% at 5 years), however the difference was not statistically significant (P=0.063).

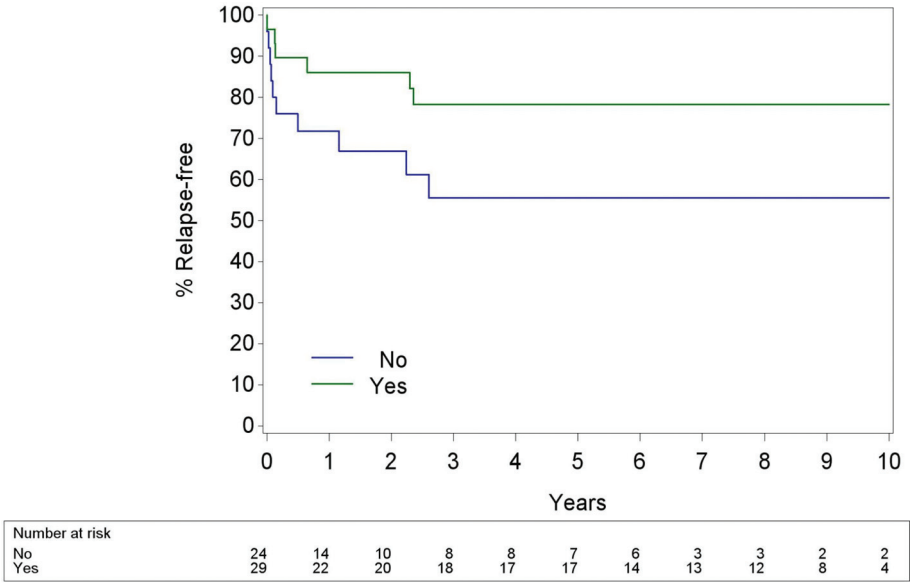

Figure 6. Kaplan-Meier estimates for overall survival shows equal survival for group with circumferential versus non-circumferential superior mesenteric artery stenosis (P=0.64).

related to in-stent restenosis, potential alternatives to bare metal stenting (BMS) have been proposed, including covered stents [21] or drug-eluting stents (DES) [22]. In a retrospective, comparative study by Oderich et al. [21] a significantly superior patency rate at 3 years of follow-up in favor of covered stents (92%±4% for covered stents versus 50%±5% for BMS) was demonstrated and Girault et al. [23] very recently found 76%, 95% and 95% primary, primary-assisted and secondary patency rates at 2 years of follow-up for covered stents in SMA occlusive disease. In addition, a multicenter, randomized trial of covered versus bare metal stents for chronic mesenteric ischemia is underway [24]. However, no difference was found in a prospective, comparative study of BMS versus DES in patients with renal artery stenosis [25]; the techniques of renal artery and mesenteric artery stenting, including the types of wires, angioplasty balloon and stents used, are very similar. However, in renal artery stenting, smaller stent-diameter is associated with a higher risk of restenosis id covered stents are used [26], but not when drug-eluting stents are inserted [27]. No similar data are available for SMA-stenting.

Long-term estimated survival after SMA-angioplasty and stenting was 82%, 57% and 28% after 2, 5 and 10 years of follow-up respectively, which is in line with the survival data of other centres, as summarized in ESM 7.

This study demonstrated a trend towards longer time to symptom relapse in patients with circumferential

SMA-stenosis compared to patients with a focal, non-circumferential stenosis (P=0.063). These findings may be in line with in vitro findings described by Ladisa et al. [28]. In a time-dependent 3D computational fluid dynamics model, these researchers found that higher cell density gradients and neointimal hyperplasia developed in regions with non-uniform shear stress. Differences in the shape of the stenosis might alter the distribution of stress along the vessel wall, which could influence the long-term stability of the stenosis, depending on its configuration [29]. However, these hypotheses need to be confirmed by prospective data.

Limitations

Finally, this study has some limitations, including its retrospective nature covering a long time interval (1999–2018), the use of various different types of stents, including over-the-wire 0.035 and rapid-exchange 0.014 inch technology, with various lengths and diameters. In addition, concommitant occlusion of the celiac trunk and inferior mesenteric artery were not assessed in this study. Patency or occlusion of these visceral arteries might influence durability of symptoms relief and patency of the SMA-stent. Lastly, follow-up in this study was based only on clinical assessment, with no routine follow-up imaging of visceral arteries and finally, the cause of death in 10 patients was unknown, potentially increasing the total number of deaths related to restenosis or thrombotic occlusion of the SMA-stent.

Conclusions

This retrospective study, focusing on the long-term outcome of angioplasty and stenting of symptomatic SMA stenosis in a substantial number of patients over a long time period, demonstrates high efficacy accompanied by a low complication rate. Recurrent symptoms related either to in-stent restenosis or to further progression of the atherosclerotic disease remain the major drawback, with an incidence of 30% at a mean follow-up of 45 months. Angioplasty and stenting of circumferential stenosis might be associated with better outcomes compared to patients with focal, non-circumferential stenosis.

Electronic supplementary material

The electronic supplementary material (ESM) is available with the online version of the article at https://doi.org/10.1024/0301-1526/a000964

ESM 1. Patients' comorbidities (Table)

ESM 2. Pre-interventional imaging modality over the years (Table)

ESM 3. Procedure-related complications (Table)

ESM 4. Cause of death in 35 patients (Table)

ESM 5. Demographic and Interventional parameters potentially predicting early or late restenosis (Table)

ESM 6. Overview of technical and short-term outcome after SMA angioplasty and stenting based on recent, high-volume studies (Table)

ESM 7. Long-term outcome data of SMA angioplasty and stenting based on recent, high volume studies (Table)

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ORCID
Geert Maleux
https://orcid.org/0000-0003-0598-0258

Correspondence address
Prof. Geert Maleux
Department of Radiology
University Hospitals Leuven
Herestraat 49
3000 Leuven
Belgium

geert.maleux@uzleuven.be

Original communication

Association between circulating Galectin-3 and arterial stiffness in older adults

Atherosclerosis Risk in Communities (ARIC) Study

Xiaoming Jia[1], Caroline Sun[1], Hirofumi Tanaka[2], Mahmoud Al Rifai[1], David Aguilar[3], Chiadi Ndumele[4], Elizabeth Selvin[4], Salim S. Virani[1,5], Ron C. Hoogeveen[1], Gerardo Heiss[6], Christie M. Ballantyne[1], and Vijay Nambi[1,5]

[1] Baylor College of Medicine, Houston, TX, USA
[2] University of Texas at Austin, Austin, TX, USA
[3] University of Texas Health Science Center at Houston, TX, USA
[4] Johns Hopkins University, Baltimore, MD, USA
[5] Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX, USA
[6] University of North Carolina at Chapel Hill, NC, USA

Summary: *Background:* Galectin-3 (gal-3) is a β-galactoside-binding lectin associated tissue fibrosis and inflammation. There is limited understanding of the relationship between gal-3 and vascular health. Our aim was to assess the association between gal-3 and arterial stiffness in older adults. *Methods:* We conducted a cross-sectional study of 4275 participants (mean age of 75 years) from the Atherosclerosis Risk in Communities (ARIC) Study. Central arterial stiffness was measured by carotid-femoral pulse wave velocity (cfPWV). We evaluated the association of gal-3 with cfPWV using multivariable linear regression. *Results:* The median (interquartile range) gal-3 concentration was 16.5 (13.8, 19.8) ng/mL and mean cfPWV was 1163±303 cm/s. Higher gal-3 concentration was associated with greater central arterial stiffness after adjustment for age, sex, race-center, heart rate, systolic blood pressure, anti-hypertensive medication use, and current smoking status (β=36.4 cm/s change in cfPWV per log unit change in gal-3; 95% CI: 7.2, 65.5, p=0.015). The association was attenuated after adjusting for additional cardiovascular risk factors (β=17.3, 95% CI: −14.4, 49.0). *Conclusions:* In community-dwelling older adults, gal-3 concentration was associated with central arterial stiffness, likely sharing common pathways with traditional cardiovascular risk factors.

Keywords: Galectin-3, arterial stiffness, aging

Introduction

Galectin-3 (gal-3) is a β-galactoside-binding lectin that is associated with pathophysiologic processes including inflammation, fibrosis and metabolic disorders. Recently, there has been an increased interest in gal-3 as a biomarker for cardiovascular disease as mounting evidence suggests that increased concentrations are associated with heart failure (HF), atrial fibrillation, atherosclerosis, pulmonary hypertension, and adverse cardiovascular outcomes [1, 2, 3, 4, 5, 6, 7]. The role of gal-3 in modulating pathways of inflammation and fibrosis makes it an interesting candidate in the study of myocardial and vascular remodeling, especially pertaining to patients with HF and hypertension [8, 9]. While elevated biomarker levels are known to be associated with these conditions, the relationship between gal-3 and arterial stiffness is less well understood [10].

Progression of arterial stiffness reflects the complex interplay of age-related vessel remodeling and oxidative stress, inflammation and vascular strain from hypertension or metabolic derangement [11, 12]. Central arterial stiffness as measured by aortic pulse wave velocity has been associated with an increased risk for cardiovascular events and all-cause mortality [13, 14, 15]. There have been a few studies assessing the association between gal-3 and arterial stiffness; Libhaber et al. showed that gal-3 was independently associated with aortic stiffness as measured by carotid-femoral pulse wave velocity (cfPWV) in 966 black community participants from South Africa with a mean age of 43.4 years [16]. Smaller studies have also shown significant associations between gal-3 and arterial stiffness in patients with prevalent HF and those on hemodialysis [17, 18]. Data is limited on the relationship between gal-3 and arterial stiffness in older age, when vascular

pathologies most often manifests. In this analysis of participants in the Atherosclerosis Risk in Communities (ARIC) study, we aim to evaluate the cross-sectional relationship between gal-3 and arterial stiffness in community-dwelling older white and black adults without prevalent HF in order to better understand the role of gal-3 in vascular aging as well as to assess gal-3 as a surrogate biomarker for arterial stiffness independent of traditional cardiovascular risk factors.

Material and methods

Patients

The ARIC study is a prospective, population cohort of adults who were middle-aged (aged 45–64 years at visit 1) when recruited from 4 US communities between 1987 and 1989. Patients were followed during multiple subsequent study visits. The study protocol was approved by the institutional review boards of all participating centers, and all participants provided written informed consent. For the present analysis, of the 6,538 individuals who participated in ARIC visit 5 (2011–2013), we excluded those with missing gal-3 measurements (N=130); those missing cfPWV or with evidence of biased PWV waveforms (N=1033), those of race other than white or black (N=18); black race at the Minneapolis and Washington County centers due to small numbers (N=24); history of aortic aneurysms (N=99); history of aortic or peripheral revascularization or graft (N=46); moderate or greater aortic stenosis (peak velocity across the aortic valve of >3 m/s) (N=27); moderate or greater aortic insufficiency (determined by visual estimation on echocardiography) (N=25); body mass index (BMI)≥40 (N=233); prevalent HF at visit 5 (N=376); and missing co-variates (N=222) [19]. After exclusions (Figure 1), there were 4275 participants included for analyses. Prevalent HF was defined as signs and symptoms of HF by the Gothenberg criteria at visit 1 or adjudicated HF hospitalization between ARIC visit 1 and visit 5 as determined by ICD-9 code 428 [20]. Medical history, demographic data, anthropometric data, blood pressure measurements, and lipid measurements were obtained at visit 5. Hypertension was defined by systolic blood pressure (SBP) ≥140 mm Hg, diastolic blood pressure (DBP) ≥90 mm Hg or reported use of antihypertensive medications. Mean arterial pressure was calculated as 1/3 SBP+ 2/3 DBP. Diabetes mellitus was defined as either self-reported diabetes diagnosed by a physician, use of hypoglycemic medications, non-fasting serum glucose levels ≥200 mg/dL, or fasting serum glucose level ≥126 mg/dL [21]. Estimated glomerular filtration rate (eGFR) was based on the creatinine-based Chronic Kidney Disease Epidemiology Collaboration Equation. Prevalent peripheral artery disease (PAD) at visit 5 was defined as having prevalent PAD at visit 4, incident PAD between visit 4 and visit 5, or ankle-brachial index (ABI) <0.9 at visit 5, where ABI was determined as the ratio of the ankle SBP to brachial SBP using the higher value of the right or left brachial SBP as the denominator [22].

Galectin-3 and other biomarker measurements

Gal-3 was measured using a chemiluminescent immunoassay on an Architect *i* 2000sr platform (Abbott, Abbott Park, IL) from EDTA-plasma samples. Samples were collected at ARIC visit 5 and were stored at −70°C before measurement (March 2017–December 2017). The limit of detection for the assay was 1.1 ng/mL and limit of quantitation was 4.0 ng/mL. Interassay coefficients of variation were 5.2%, 3.3%, and 2.3% at mean galectin-3 levels of 8.8 ng/mL, 19.2 ng/mL, and 72.0 ng/ml, respectively. The reliability coefficient was r=0.92. The coefficient of variation was 7.5% based on 402 blinded quality-control samples.

High-sensitivity C-reactive protein (hs-CRP) was measured by using an immunonephelometric assay on a BNII autoanalyzer (Siemens Healthcare Diagnostics, Deerfield, Illinois) with a reliability coefficient of 0.99 [23].

Pulse wave velocity measurements

Detailed descriptions of measurement and quality assurance of cfPWV in ARIC has been described previously [24]. Briefly, carotid-femoral PWV was measured following a standardized protocol with the automated waveform analyzer VP-1000 Plus (Omron, Kyoto, Japan). A minimum of 2 measurements were taken per participant and the last 2 measurements were averaged.

Statistical analysis

Baseline characteristics for the study population at visit 5 were tabulated by quartiles of gal-3 concentration. P-values for linear trend across gal-3 quartiles were calculated using test of trend. Gal-3 was evaluated as a continuous variable (natural log transformed due to non-normality) and as a categorical variable grouped by quartiles (quartile 1 as the reference group). Linear regression analyses were performed to assess the cross-sectional association between visit 5 gal-3 and cfPWV treated as a continuous variable. The beta-coefficient from the linear coefficient is expressed as cm/s change in cfPWV per log unit change in gal-3. Logistic regression analyses were also performed to assess the association between gal-3 and cfPWV treated as a categorical variable (≥75 percentile vs <75 percentile as the reference). Stepwise adjustment models were constructed with co-variates selected a-priori, first accounting for likely confounders (models 1 and 2) and then including covariates that may be potential modifiers (model 3). Model 1 adjusted for age, sex, race-center while model 2 adjusted for model 1 plus heart rate, SBP, anti-hypertensive medication use, current smoking status and finally model 3 adjusted for model 2 plus diabetes status, low-density

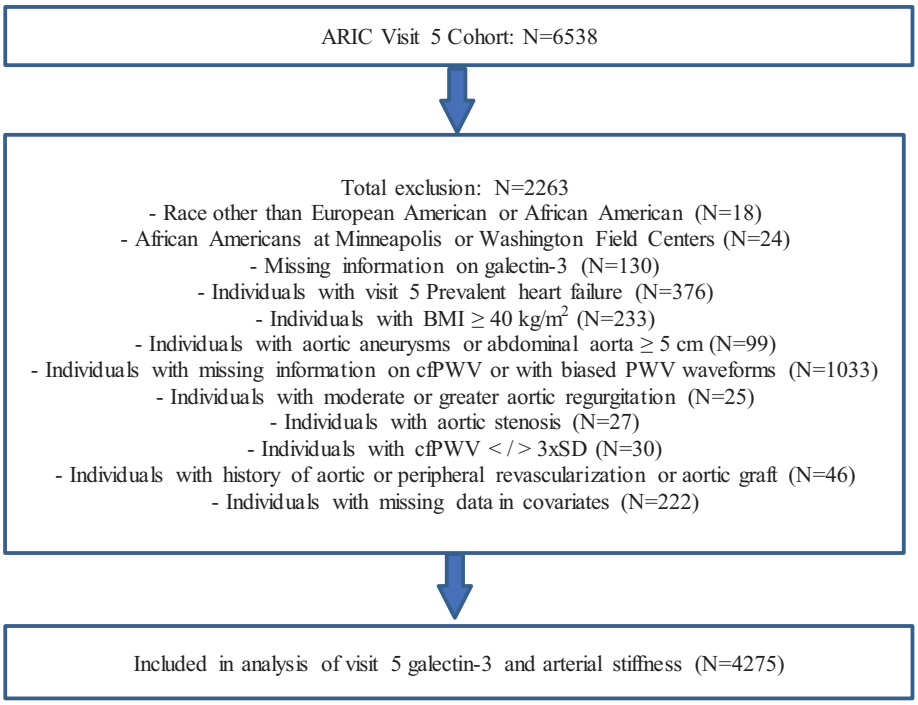

Figure 1. Inclusion and exclusion criteria.

lipoprotein cholesterol (LDL-C), eGFR, hs-CRP, and body mass index (BMI). We then performed stratified analyses with respect to sex, race, diabetes status, hypertension status, inflammation status (based on hs-CRP <2mg/L vs ≥2mg/L), and prevalent PAD to evaluate whether these factors may be effect modifiers of the association between gal-3 and cfPWV.

Results

Baseline characteristics of participants at visit 5 across gal-3 quartiles are shown in Table I. The mean age at visit 5 was 75.2±5.0 years and 59.5% were women. The median (interquartile range) gal-3 level at visits 5 was 16.5 (13.8, 19.8) ng/mL while the mean cfPWV at visit 5 was 1163± 303 cm/s. Overall, individuals with higher gal-3 at visit 5 were more likely to be older, female, black, have higher pulse pressure, heart rate, BMI; were more likely to be users of anti-hypertensive and cholesterol lowering medication, and were more likely to have hypertension, diabetes and prevalent coronary heart disease. Higher gal-3 was also associated with lower DBP, mean arterial pressure, LDL-C and eGFR. Finally, higher gal-3 categories were associated with higher frequencies of prevalent PAD.

When analyzed as a continuous variable, higher gal-3 was significantly associated with greater central arterial stiffness as measured by cfPWV after adjustments for model 1 (β=53.9 cm/s change in cfPWV per log unit change in gal-3, 95% CI: 22.8, 85.0, p=0.001) and model 2 covariates (β=36.4, 95% CI: 7.2, 65.5, p=0.015). However, the association was attenuated and became statistically non-significant after additional adjustments with model 3 covariates (β=17.3, 95% CI: −14.4, 49.0).

In an analysis stratified by diabetes status, there was a significant association between gal-3 and arterial stiffness observed in adults without diabetes (β=35.1, 95% CI: 0.8, 69.3, p=0.045) and without hypertension (β=73.9, 95% CI: 19.5, 128.2, p=0.008) subgroups up to model 2 adjustment but not in their respective subgroups with disease. The association was attenuated after model 3 adjustment (β=24.9, 95% CI: −12.1, 61.9, p=0.186 for individuals without diabetes; β=52.2, 95% CI: −3.72, 108.1, p=0.067 for individuals without hypertension). In the subgroup of participants without both diabetes and hypertension, there was a significant association between gal-3 and arterial stiffness even after adjustment for model 3 (β=67.2, 95% CI: 9.2, 125.3, p=0.023). However, the p-interaction was not significant. Finally, there was significant association in the non-prevalent PAD subgroup up to model 2 adjustment (Table II). There were no significant differences in association noted between white and black race or for any other subgroups (all p-interaction >0.05).

When treating gal-3 as a categorical variable, there was not a consistent association between higher categories of gal-3 with cfPVW. For instance, there was a statistically significant association between higher levels of gal-3 with cfPWV after model 1 adjustment when comparing Quartile 3 vs Quartile1 (β=30.9, 95% CI: 6.0, 55.7), but Quartile 4 vs Quartile 1 was not significant (β=23.9, 95% CI: −1.6, 49.4). There was also no significant association between quartiles of gal-3 with cfPWV after adjustments with model 2 and model 3 covariates (data not shown).

In logistic regression analysis, there was a significant association between higher gal-3 with increased odds of ≥75 percentile vs <75 percentile cfPWV after model 2 adjustment (OR: 1.42, 95% CI: 1.07, 1.88, p=0.014).

Table I. Baseline characteristics across galectin-3 quartiles at visit 5 of the ARIC Study

	Visit 5 galectin-3 quartiles (ng/mL)				
	Q1 (4.2–13.8)	Q2 (13.9–16.5)	Q3 (16.6–19.8)	Q4 (19.9–94.3)	P trend
cfPWV (cm/s)	1128±293.2	1155±294.8	1177±301.0	1188±319.3	<0.001
Age (year)	74.3±4.9	74.6±4.6	75.5±5.0	76.5±5.3	<0.001
Female %	46.8	57.2	63.5	70.7	<0.001
Black %	16.0	19.9	23.6	27.9	<0.001
SBP (mmHg)	129.5±17.1	130.2±16.9	130.5±17.3	130.0±18.3	0.297
DBP (mmHg)	67.1±10.3	66.8±10.1	66.6±10.5	64.6±10.4	<0.001
Pulse pressure (mmHg)	62.4±13.7	63.4±13.7	63.9±14.1	65.4±15.1	<0.001
Mean arterial pressure (mmHg)	87.9±11.3	87.9±11.1	87.9±11.4	86.4±11.5	0.003
Heart beat (beat/min)	64.1±10.8	65.1±10.7	65.6±10.9	65.6±11.1	0.001
Hypertensive medication %	59.7	69.7	72.9	86.4	<0.001
Hypertension %	62.6	70.4	72.8	83.7	<0.001
BMI (kg/m^2)	27.2±4.3	27.6±4.4	27.8±4.5	28.6±4.6	<0.001
Diabetes (%)	26.1	23.1	30.5	36.3	<0.001
LDL-C (mg/dL)	108.3±32.9	107.1±33.9	106.8±35.7	102.0±34.8	<0.001
Cholesterol lower medication (%)	48.4	53.8	54.9	62.6	<0.001
Current smoking (%)	6.0	5.0	6.1	5.6	0.982
eGFR (mL/min/1.73 m^2)	77.7±13.1	73.9±14.2	70.9±15.0	61.2±18.3	<0.001
hs-CRP (mg/L)	1.5 (0.8, 3.1)	1.8 (0.9, 3.6)	1.9 (0.9, 3.9)	2.3 (1.1, 4.7)	<0.001
Prevalent CHD (%)	9.7	12.0	11.6	14.6	0.001
Prevalent PAD (%)	4.3	6.8	8.8	14.1	<0.001

Data presented as mean±SD, median (25th, 75th percentile), or percentage; P trend were calculated by test of trend across ordered groups. cfPWV: carotid-femoral pulse wave velocity; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; LDL-C: low-density lipoprotein cholesterol; eGFR: estimated glomerular filtration rate; CHD: coronary heart disease; hs-CRP: high-sensitivity C-reactive protein; PAD: peripheral artery disease.

The association was attenuated after additional adjustments with model 3 covariates (OR: 1.21, 95% CI: 0.89, 1.65) (Table III). There was a significant odd for elevated cfPWV when comparing quartile 4 with quartile 1 gal-3 after model 1 adjustment (OR: 1.25, 95% CI: 1.01, 1.55). But the association between quartiles of gal-3 with cfPWV was attenuated after adjustments with model 2 and model 3 covariates (data not shown).

Discussion

In this analysis of the association between circulating gal-3 levels with central arterial stiffness in older adults, we found that gal-3 was significantly associated with cfPWV after adjustment for age, sex, race-center, heart rate, SBP, antihypertensive medication use, and current smoking status. However, the association was attenuated and became non-significant after further adjustment for additional cardiovascular risk factors including diabetes, LDL-C, eGFR, hs-CRP, and BMI. The association of gal-3 with arterial stiffness appeared to be stronger in subgroups of participants without hypertension and diabetes. The results suggest that gal-3 demonstrate significant association with arterial stiffness in older adults, but this relationship likely shares common pathways, and thus are not independent of other cardiovascular risk factors such as diabetes and hypertension.

Our results differ from data from previous studies that showed significant association between circulating gal-3 levels and arterial stiffness even after adjustment of multiple cardiovascular risk factors [16, 17, 18]. The differences may be due to a difference in the study population. Notably, individuals included in our study were older, of white and black race who did not have prevalent HF, which differs from those that were examined in prior studies: younger patients of black race, patients with HF and end-stage renal disease on dialysis. Our results therefore build upon findings of previous studies and suggest that while gal-3 demonstrate significant association with arterial stiffness in selected patient populations, this relationship is likely not independent of traditional cardiovascular risk factors in older adults.

Gal-3 levels were (positively) correlated with risk factors such as hypertension and diabetes, suggesting that gal-3 may be a potential marker, or mediator between these risk factors and arterial stiffness. Though higher gal-3 levels were correlated with decreased DBP, this is likely reflective of the widening pulse pressure observed, another marker of arterial stiffness. A correlation with lower MAP is likely related to lower DBP as well as the increased use of antihypertensive medication in these patients. Likewise, the lower LDL-C noted in the higher gal-3 categories likely reflect an increase in cholesterol lowering medication use among these patients who have higher risk for CVD. Risk factors such as hypertension and diabetes contribute to endothelial dysfunction, inflammation and vascular

Table II. Linear regression showing the association of visit 5 galectin-3 as a continuous variable (natural log transformed) and arterial stiffness as measured by visit 5 carotid-femoral pulse wave velocity in the overall included participants as well as by subgroups

	B coefficient	95% CI	P value
Overall (N=4275)			
Model 1	53.9	22.8, 85.0	**0.001**
Model 2	36.4	7.2, 65.5	**0.015**
Model 3	17.3	−14.4, 49.0	0.285
Men (N=1731)			
Model 1	81.6	31.8, 131.5	**0.001**
Model 2	46.1	−1.1, 93.3	0.055
Model 3	26.5	−25.1, 78.1	0.314
Women (N=2544)			
Model 1	34.4	−5.3, 74.2	0.090
Model 2	28.5	−8.6, 65.7	0.132
Model 3	11.9	−28.4, 52.2	0.563
Whites (N=3342)			
Model 1	51.8	17.9, 85.8	**0.003**
Model 2	27.4	−4.5, 59.4	0.093
Model 3	5.6	−28.7, 39.8	0.751
Blacks (N=933)			
Model 1	60.8	−13.3, 134.9	0.108
Model 2	68.9	−0.2, 138.1	0.051
Model 3	62.0	−16.8, 140.9	0.123
Non-diabetics (N=3037)			
Model 1	52.0	15.4, 88.5	**0.005**
Model 2	35.1	0.8, 69.3	**0.045**
Model 3	24.9	−12.1, 61.9	0.186
Diabetes (N=1238)			
Model 1	14.9	−43.2, 72.9	0.615
Model 2	24.2	−30.7, 79.2	0.387
Model 3	3.2	−58.2, 64.6	0.918
Non-hypertension (N=1176)			
Model 1	109.2	51.7, 166.8	**<0.001**
Model 2	73.9	19.5, 128.2	**0.008**
Model 3	52.2	−3.7, 108.1	0.067
Hypertension (N=3073)			
Model 1	12.5	−24.5, 49.6	0.507
Model 2	25.0	−9.7, 59.6	0.158
Model 3	7.9	−30.4, 46.2	0.685
Non-hypertension and non-diabetes (N=975)			
Model 1	103.4	44.2, 162.6	**0.001**
Model 2	72.8	16.7, 128.9	**0.011**
Model 3	67.2	9.2, 125.3	0.023
Hypertension or diabetes (N=3281)			
Model 1	18.0	−18.0, 54.0	0.327
Model 2	26.9	−7.0, 60.9	0.120
Model 3	4.6	−32.7, 42.0	0.808
hs-CRP<2 mg/L (N=2289)			
Model 1	59.9	18.4, 101.4	**0.005**
Model 2	32.0	−7.0, 71.0	0.108
Model 3	22.0	−19.9, 63.9	0.304
hs-CRP≥2 mg/L (N=1986)			
Model 1	29.7	−17.2, 76.6	0.214
Model 2	16.2	−8.0, 80.4	0.108
Model 3	9.8	−38.6, 58.3	0.691
Non-prevalent PAD (N=3905)			
Model 1	45.3	13.0, 77.6	**0.006**
Model 2	32.2	1.9, 62.5	**0.037**
Model 3	11.7	−20.9, 44.3	0.483
Prevalent PAD (N=363)			
Model 1	71.7	−46.0, 189.3	0.232
Model 2	29.7	−82.4, 141.8	0.603
Model 3	53.3	−79.2, 185.8	0.429

Model 1: Adjusted by v5 age, gender, and race-center. Model 2: model 1 plus v5 heart rate, anti-hypertensive medication user, current smoking, and SBP. Model 3: model 2 plus LDL-C, eGFR, BMI, diabetes status and hs-CRP. Bold values indicate statistical significance (p<0.05).

Table III. Logistic regression with visit 5 gal-3 as a continuous as the independent variable and visit 5 cfPWV as dependent variable treated as dichotomous variable (>75 percentile of cfPWV vs <75 percentile as reference)

	Odds ratio	95% CI	P value
Model 1	1.52	1.17–1.96	0.001
Model 2	1.42	1.07–1.88	0.014
Model 3	1.21	0.89–1.65	0.218

Model 1: Adjusted by v5 age, gender, and race-center. Model 2: model 1 plus v5 heart rate, anti-hypertensive medication user, current smoking, and SBP. Model 3: model 2 plus LDL-C, eGFR, BMI, diabetes status and hs-CRP.

fibrosis [25, 26]. These risk factors may induce increased expression of gal-3, a known modulator of inflammation and fibrosis, in activated macrophages, endothelial and vascular smooth muscle cells ultimately leading to pathological vascular remodeling [27]. Meanwhile, in the absence of hypertension and diabetes, gal-3 may represent a marker for unexplained vascular stiffness. More detailed mechanism by which these co-morbidities relate to gal-3 and vascular health deserves further investigation.

Age may also be an important modifier in the relationship between gal-3 and arterial stiffness. Both gal-3 levels and arterial stiffness measures are lower at younger age. For instance, in the study by Libhaber et al (mean age ~43 years), the mean gal-3 level was 8.88 (SD=4.02) and the mean cfPWV was 6.43 (SD=2.69), thus much lower than those observed in our study [16]. Elevated gal-3 may reflect ongoing vascular remodeling. In younger age, the ability of gal-3 to identify increased arterial stiffness may be relatively larger as risk factors for vascular health such as hypertension and diabetes are less prevalent and exposure time to these risk factors is shorter. For instance, we found that gal-3 was more significantly associated with arterial stiffness in individuals without hypertension and diabetes (but less so among those with these conditions). As gal-3 appears to be significantly correlated with traditional cardiovascular risk factors, prolonged exposure to these risk factors with aging likely attenuates the effects of gal-3 as an independent biomarker of arterial stiffness. Furthermore, gal-3 may reflect vascular pathogenesis,

a process that may not be as robust in older age when subclinical or clinical vascular disease is more likely to have already established.

A study of gal-3 from an earlier visit from the ARIC study found that gal-3 was significantly associated with incident PAD independent of traditional cardiovascular risk factors [28]. In our current analysis, gal-3 was also associated with an increased frequency of prevalent PAD. Interestingly, the median levels of gal-3 of included patients in our analysis (median gal-3 of 16.5 ng/mL) was numerically similar to those individuals with incident PAD (median gal-3 of 16.9 ng/mL) in the previous ARIC analysis. However, the participants were more than a decade older in our current analysis. Taken together, gal-3 appears to contribute to development of arterial pathology as reflected by increased risk of PAD at earlier age as well as central arterial stiffening in older adults.

Limitations

There are some limitations to our study. While we measured galectin-3 in blood, it remains unclear how circulating biomarkers reflect tissue specific expression and future studies to clarify this relationship are needed. Also, as this was an observational study, there is possibility of residual confounding and selection bias.

Conclusions

In this study, circulating blood levels of gal-3 was significantly associated with central arterial stiffness in older adults. However, our results suggest that this association is not independent of traditional cardiovascular risk factors and that gal-3 likely shares common pathways with risk factors such as hypertension and diabetes in the development of arterial stiffness in older age.

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Conflict of interest
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ORCID
Xiaoming Jia
https://orcid.org/0000-0001-7949-6173

Vijay Nambi, MD/PhD
Baylor College of Medicine
1 Baylor Plaza, 521D, MS 285
Houston, TX 77030
USA

vnambi@bcm.edu

Original communication

The prospective GermanVasc cohort study

Endovascular and open-surgical treatment of symptomatic peripheral artery disease

Artur Kotov[1], Frederik Peters[1], Eike Sebastian Debus[1], Thomas Zeller[2], Peter Heider[3], Konstantinos Stavroulakis[4], Jürgen Remig[5], Andreas Gussmann[6], Johannes Hoffmann[7], Oliver Friedrich[8], Thomas Nolte[9], and Christian-Alexander Behrendt[1]

[1] University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[2] University Heart Center Freiburg-Bad Krozingen, Germany
[3] Isar Clinic Munich, Germany
[4] St. Franziskus Hospital GmbH, Münster, Germany
[5] Bonn Community Hospital, Haus St. Petrus, Bonn, Germany
[6] HELIOS Clinical Centre Berlin-Buch, Berlin, Germany
[7] Contilia Elisabeth-Hospital Essen, Germany
[8] GFO Clinics Bonn Operating St. Marien, Bonn, Germany
[9] Bad Bevensen Heart and Vascular Centre, Bad Bevensen, Germany

Summary: *Background:* Previous observational studies reported a wide variation and possible room for improvement in the treatment of patients suffering from symptomatic peripheral artery disease (PAD). Yet, systematic assessment of everyday clinical practice is lacking. A General Data Protection Regulation (GDPR) compliant registry was developed and used to collect comprehensive data on clinical treatment and outcomes regarding PAD in Germany. Here, we report baseline characteristics of patients prospectively enrolled until the end of 2020. *Methods:* The GermanVasc registry study is a prospective longitudinal multicentre cohort study. Between 1st May 2018 and 31st December 2020, invasive endovascular, open-surgical, and hybrid revascularisations of patients suffering from chronic symptomatic PAD were prospectively included after explicit informed consent (NCT03098290). For ensuring high quality of the data, we performed comprehensive risk-based and random-sample external and internal validation. *Results:* In total, 5608 patients from 31 study centres were included (34% females, median 69 years). On-site monitoring visits were performed at least once in all centres. The proportion of chronic limb-threatening ischaemia was 30% and 13% were emergent admissions. 55% exhibited a previous revascularisation. Endovascular techniques made 69% among all documented invasive procedures (n=6449). Thirty-five percent were classified as patients with severe systemic disease, and 3% exhibited a constant threat to life according to the American Society of Anaesthesiologists classification. The risk profile comprised of 75% former or current smokers, 36% diabetes mellitus, and in 30% a current ischemic heart disease was present. At discharge, 93% of the patients received antiplatelets and 77% received statins. *Conclusions:* The GermanVasc registry study provides insights into real-world practice of treatment and outcomes of 5,608 patients with symptomatic PAD in Germany. The cohort covers a broader range of disease severity and types of interventions than usually found in trials. In future studies, comparative outcomes will be analysed in more detail.

Keywords: Health services research, peripheral artery disease, intermittent claudication, chronic limb-threatening ischaemia, endovascular techniques, bypass surgery

Introduction

Although peripheral artery disease (PAD) is a common illness with more than 230 million affected worldwide, the existing evidence base to treat this target population is still incomplete in regard of patient selection, best medical treatment, and the best patient-centred approach to revascularise atherosclerotic lesions [1].

A wide variation between countries was previously reported concerning the proportion of patients with claudication, endovascular techniques, females, and octogenarians [2]. In line with this unexplained variation, nearly half of all recommendations in valid practice guidelines are based on low level of evidence [3, 4, 5].

While the vascular community waits with bated breath for the first results of currently recruiting randomized

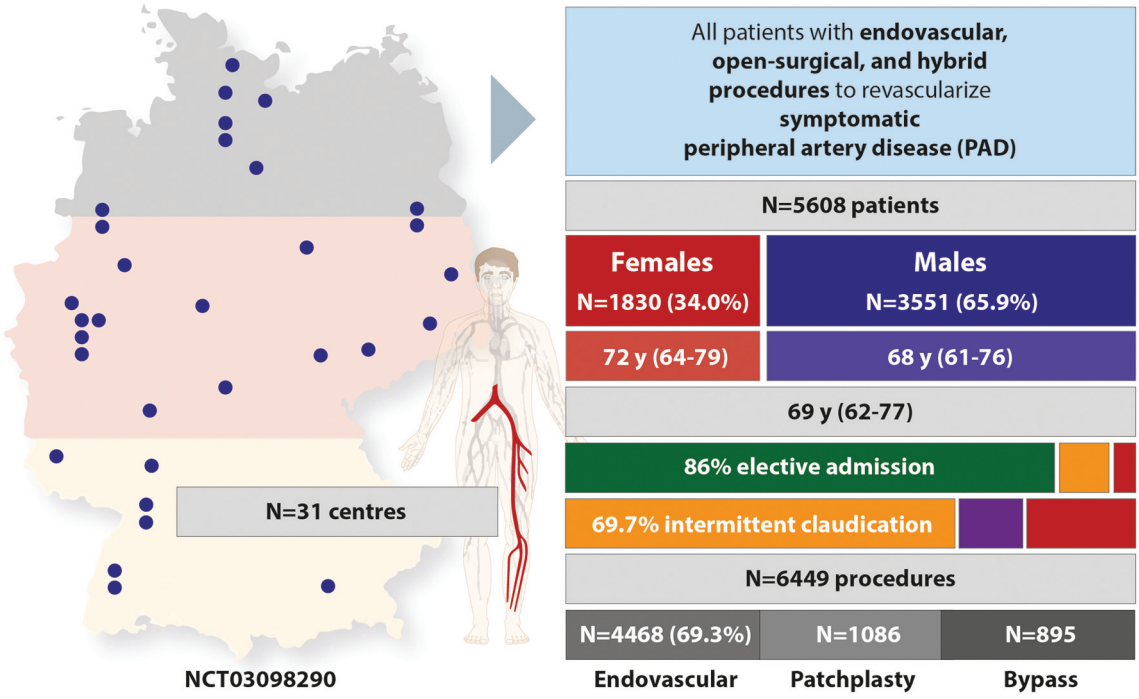

Figure 1. Central Illustration of this prospective multicentric cohort study of 5608 patients.

controlled trials (RCT) [6, 7], it appears reasonable to match conclusions derived from RCTs with high quality registry data better reflecting everyday clinical practice. For instance, in an ongoing debate concerning outcomes after drug-coated device treatment, RCTs reported excess long-term mortality while real-world data showed opposite results, emphasizing their complementary value [8, 9]. While health insurance claims data offer particularly large samples for such purpose, clinical registries additionally offer the inclusion of more detailed parameters such as body mass index, lesion characteristics, blood pressure, and ankle-brachial-index.

The GermanVasc study included patients with symptomatic PAD who underwent either endovascular, open-surgical, or hybrid revascularisations between 1st May 2018 and 31st December 2020 at 31 German centres (Figure 1). The rationale and methods were published and registered a priori (clinicaltrials.gov NCT03098290) [10, 11]. All indicators of outcome quality and additional variables collected in the current study were aligned by international Delphi consensus methods [12, 13, 14]. The data collection underwent both an independent random-sample validation and automated quality assurance.

The primary goal of the study was to quantify to which extent real-world treatment follow guideline recommendations.

The current report aims to present the baseline characteristics of the included patients.

Material and methods

This was a prospective longitudinal multicentre cohort study. The rationale and methods of the GermanVasc registry study were published a priori [10, 11] and additionally registered at Clinicaltrials.gov (NCT03098290) and the German Registry of Clinical Trials (DRKS00014649). A total of 18 ethical committees in affected German federal states confirmed the initial approval by the leading ethical committee at the medical association in Hamburg, Germany (PV5691). The European Union (EU) General Data Protection Regulation (GDPR) compliant GermanVasc registry platform was developed to follow the principles of privacy by design while collecting the personal and medical data relevant for the current study [11, 15, 16]. Results were reported using the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement [17].

Inclusion and exclusion criteria

All patients above 18 years who underwent either endovascular, open-surgical, or hybrid revascularisation for chronic symptomatic PAD between 1st May 2018 and 31st December 2020 at participating study centres were included if an explicit informed consent was available by the data subject. Patients with embolic acute limb ischaemia without history of chronic PAD were excluded. According to the modified Rutherford classification, patients selected for invasive revascularisation with mild, moderate, and severe claudication were pooled as intermittent claudication (IC). Patients selected with ischaemic rest pain, ulcer or necrosis, and non-healing amputation were pooled as chronic limb-threatening ischaemia (CLTI).

Study variables

The data collection in the current study followed three previous Delphi consensus studies on registry core elements and quality indicators for peripheral arterial revascularisation. These study variables were published

elsewhere [12, 13, 14]. Variables were collected at baseline, after three, six, and twelve months of follow-up. In the current report, we present baseline characteristics as follow-up data collection is still ongoing.

In short, the following medical variables were collected during the baseline treatment: Age (years), sex (male, female, transgender), admission month and weekday, discharge month and weekday, urgency of the admission, living status, functional status, ambulation, discharge destination, weight (kilogram), height (meter), body mass index (BMI, calculated as kg/m^2), American Society of Anaesthesiologists (ASA) class, diabetes mellitus, glycohaemoglobin, renal insufficiency, most recent serum creatinine, current dialysis dependency, tobacco use (active, former), years since last smoking, current ischaemic heart disease, congestive heart failure, ejection fraction, cardiac arrhythmia, history of atrial fibrillation, chronic obstructive pulmonary disease (COPD), hypertension, prior peripheral arterial disease revascularisation, prior lower leg amputations, antiplatelets at the time of admission and at discharge, statins at the time of admission and at discharge, PCSK9-inhibitor at the time of admission and at discharge, vitamin K antagonist at the time of admission and at discharge, new/direct oral anticoagulants at the time of admission and at discharge, modified Rutherford classification (per side), foot infection (per side), ankle-brachial-index (ABI, per side, categorised), tissue loss (per side), postoperative myocardial infarction, postoperative stroke, postoperative new dialysis dependency, postoperative ankle-brachial-index (per side, categorized), postoperative unplanned amputation (per side), postoperative occlusion of index revascularisation, postoperative distal embolization, postoperative dissection, postoperative failure of graft or device, postoperative bleeding including pseudoaneurysm, postoperative compartment syndrome, postoperative wound infection, quality of life (WIQ and SF36).

Statistical analysis

Normality of data was tested using the Shapiro-Wilk-Test. We summarized the baseline characteristics of the patients with median and interquartile range (IQR) for non-normally distributed variables with mean and standard deviation for normally distributed variables, and with percentages and Wald 95% confidence interval (CI) for categorical variables. Missing values were handled by case exclusion for each analysis.

All statistical analyses were performed with SPSS version 25 (IBM Corporation, New York, USA). Visualization was performed with Adobe Illustrator version 24.1.2 (Adobe, San Jose, CA, USA).

Results

In total, 5608 patients (34% females, median 69 years, IQR: 62–77) treated in 31 centres with 6449 procedures in total were registered from 1st May 2018 through 31st December 2020. External on-site visits were performed at least once in 100% of all study centres. Core characteristics were complete in 100% of all cases.

The baseline characteristics of the entire cohort and by occurrence of CLTI are presented in Table I. An urgent or emergent presentation at the study centre was documented in 12.5% (95% CI: 11.6–13.4). Among a total of 6449 documented procedures provided to the study cohort, 4468 (69.3%, 95% CI: 68.1–70.4) were endovascular procedures.

Among all patients, 4.9% (95% CI: 4.4–5.5) were referred from another hospital or department to the study centre, and 0.8% (95% CI: 0.6–1.1) were admitted from a nursery or rehabilitation facility. More than half of the cohort (54.9%, 95% CI: 53.5–56.2) exhibited at least one previous revascularisation of the lower extremities, and 5.5% (95% CI: 4.9–6.2) exhibited a previous major lower limb amputation before the index treatment.

In total, 4.6% (95% CI: 4.1–5.2) of the patients needed assisted care or bedridden, while 18.0% (95% CI: 17.0–19.0) were supplied with either prosthesis, assistive device, or wheelchair.

Regarding the overall physical status according to the ASA classification, 65.1% were either classified as a patient with mild systemic disease (30.6%, 95% CI: 29.4–31.8) or severe systemic disease (34.5%, 95% CI: 33.2–35.7). Among all patients, 3.1% (95% CI: 2.7–3.6) exhibited a severe systemic disease that is a constant threat to life.

Body mass index, hypertension, smoking, and diabetes

The median body mass index (BMI) of the entire cohort was 26.0 kg/m^2 (95% CI: 23.4–29.3), and 20% (95% CI: 19.0–21.1) were obese according to the threshold of 30 kg/m^2.

82.2% (95% CI: 81.1–83.2) had a history of hypertension. 44.3% (95% CI: 43.0–45.6) of the entire cohort reported current smoking at the time being selected for invasive revascularisation, and 30.7% (95% CI: 29.5–31.9) were former smoker with a median quit time of 15 years (IQR: 6–26).

35.7% (95% CI: 34.5–37.0) were diagnosed with diabetes. Among these patients, the median HbA1C value was 7 (IQR: 6–8).

Cardiac risk

One third of the cohort was diagnosed with ischemic heart disease. Among all patients, 29.5% (95% CI: 28.3–30.8) were asymptomatic at the time of presentation, 5.3% (95% CI: 4.7–5.9) exhibited angina only during physical activity, and 1.3% (95% CI: 1.1–1.7) exhibited symptoms at everyday living activities or at rest.

14.9% (95% CI: 14.0–15.9) of the patients reported any history of coronary artery revascularisation, and 16.8% (95% CI: 15.8–17.8) had a history of myocardial infarction.

Table I. Baseline characteristics of this cohort including 5608 patients with invasive revascularisation for symptomatic peripheral artery disease. If not otherwise indicated, all values are presented as percentage (%) with 95% confidence interval

	Total cohort		Chronic limb-threatening ischaemia		No chronic limb-threatening ischaemia	
Number of patients	5608		1676 (29.9%)		3932 (70.1%)	
Patient age, years (median, interquartile range)	69	62–77	72	64–80	68	61–76
Octogenarians	15.7	14.8–16.7	25.4	25.4–27.6	11.6	10.6–12.6
Females	34.0	32.7–35.3	34.3	32.0–36.7	33.8	32.3–35.4
Urgent or emergent presentation	12.5	11.6–13.4	31.7	29.5–34.0	4.2	3.6–4.9
Referred from another hospital	4.9	4.4–5.5	11.2	9.8–12.8	2.2	1.8–2.7
Admitted from nursery/rehab	0.8	0.6–1.1	2.3	1.7–3.2	0.3	0.1–0.5
Needed assisted care/bedridden	4.6	4.1–5.2	11.5	10.0–13.1	1.6	1.3–2.1
Ambulation with any assistive device or bedridden	18.0	17.0–19.0	39.4	37.0–41.8	8.7	7.9–9.7
ASA Class III	34.5	33.2–35.7	39.4	37.0–41.8	29.8	28.4–31.3
ASA Class IV	3.1	2.7–3.6	6.6	5.4–7.9	1.6	1.2–2.1
Body mass index (median, interquartile range)	26.0	23.4–29.3	25.8	22.9–29.3	26.1	23.7–29.3
Body mass index >30 kg/m^2	20.0	19.0–21.1	21.0	19.1–23.0	19.6	18.4–20.9
Diabetes mellitus	35.7	34.5–37.0	47.4	45.0–49.8	30.7	29.2–32.1
Chronic renal failure	22.1	21.0–23.2	32.5	30.2–34.8	17.7	16.5–18.9
Dialysis dependency	2.5	2.1–2.9	5.4	4.4–6.6	1.3	0.9–1.6
Current smoker	44.3	43.0–45.6	37.7	35.3–40.0	46.3	44.8–47.9
Former smoker	30.7	29.5–31.9	30.5	28.3–32.8	30.2	28.8–31.7
Quit time, years (median, interquartile range)	15	6–26	16	7–30	13	5–24
Asymptomatic ischaemic heart disease	29.5	28.3–30.8	34.2	31.9–36.5	27.5	26.1–28.9
Angina symptoms during physical activity	5.3	4.7–5.9	6.6	5.5–7.9	4.7	4.0–5.4
Angina symptoms at everyday living activities or at rest	1.3	1.1–1.7	1.7	1.2–2.5	1.2	0.9–1.6
History of coronary artery revascularisation	14.9	14.0–15.9	18.1	16.3–20.0	13.6	12.5–14.7
History of myocardial infarction	16.8	15.8–17.8	20.4	18.4–22.4	15.3	14.2–16.4
History of congestive heart failure	17.0	16.0–18.0	23.5	21.5–25.5	13.9	12.8–15.0
Ejection fraction, %	50	40–55	45	35–55	51	42–55
History of cardiac arrhythmias	18.7	17.7–19.8	23.5	21.5–25.6	14.9	13.8–16.0
History of chronic obstructive pulmonary disease	11.6	10.7–12.4	12.7	11.2–14.4	10.9	9.9–11.9
History of hypertension	82.2	81.1–83.2	74.8	73.4–76.2	81.9	79.9–83.7
History of any lower extremity revascularisation	54.9	53.5–56.2	56.1	53.7–58.5	49.3	47.8–50.9
History of any lower extremity amputation	5.5	4.9–6.2	13.4	11.8–15.1	2.1	1.7–2.6

ASA: American Society of Anaesthesiologists.

A history of congestive heart failure was reported in 17.0% (95% CI: 16.0–18.0), while a median left ventricular ejection fraction of 50% (IQR: 40–55) was documented in these patients. 18.7% (95% CI: 17.7–19.8) reported any history of clinically relevant cardiac arrhythmias.

Other risk factors

A chronic renal failure was apparent in 22.1% (95% CI: 21.0–23.2) of the cohort, while 2.5% (95% CI: 2.1–2.9) were dependent from chronic dialysis.

A chronic obstructive pulmonary disease was reported by 11.6% (95% CI: 10.7–12.4) of the patients.

Invasive procedures

A total of 6449 invasive procedures were registered. Among all registered revascularisations, 69.3% (95% CI: 68.1–70.4) were endovascular procedures (n=4468). A total of 1285 drug-coated balloons and 292 drug-eluting stents were registered. Vascular surgeons were actively involved in the procedure in 43.0% (95% CI: 41.5–44.4), interventional radiologists in 33.5% (95% CI: 32.1–34.9), and interventional internists in 34.4% (95% CI: 33.1–35.9) of the procedures. A total of 17.8% (95% CI: 16.7–19.0) of the procedures involved at least two medical specialties. 8.7% (95% CI: 7.9–9.6) of the procedures were performed as hybrid approach with cut down. In 52.6% (95% CI: 51.1–54.1) of the registered procedures, a total of 2351 closure devices were documented.

Antiplatelets and statins

At the time of admission, 84.7% (95% CI: 83.7–85.6) of the patients were on antiplatelet medication, while 67.5% (95% CI: 66.2–68.7) were taking statins. After discharge, the prescription rate of antiplatelets was 93.5% (95% CI: 92.8–94.1) and 76.5% (95% CI: 75.4–77.6) for statins.

Risk profile by occurrence of chronic limb-threatening ischaemia

Among the entire cohort, 1676 (29.9%, 95% CI: 28.7–31.1) patients presented with either ischaemic rest pain or ischaemic wound healing disorders. In CLTI patients, the proportion of octogenarians, urgent or emergent presentation, referral from another hospital, and referral from nursery or rehabilitation facilities was higher when compared with patients without CLTI symptoms (Table I). The overall risk profile was more pronounced in CLTI patients concerning higher ASA class, diabetes, chronic renal failure, cardiac disease, and previous lower extremity revascularisation or amputation.

Discussion

This large prospective observational cohort study evaluated the everyday clinical practice at 31 vascular centres in Germany. More than 5600 patients were treated by approximately 6500 endovascular and open-surgical procedures for chronic symptomatic PAD. The protocol of the current study was published a priori, and the study data underwent a rigorous validation by an external random-sample and risk-based quality assurance.

The included patients, especially those suffering from CLTI, exhibited a severe multimorbidity and multiple cardiovascular risk factors. One third of the cohort were patients with severe systemic disease, and more than three percent were in a life-threatening condition.

There is growing evidence for a wide variation of practice patterns between countries, centres, and registries. The reasons, however, are mostly unknown. In the United Kingdom, the Getting It Right First Time (GIRFT) programme identified such variations as possible room for improvement [18]. The 2018 GIRFT report found that many patients needing urgent surgery face long or uncertain waits, and a "lack of consistency in the approach taken to the same condition – with different providers choosing different surgical methods in apparently similar circumstances" [19]. Globally, a recent comparison of population-based registries in eleven countries revealed that patient selection and treatment modality varied widely for the proportion of patients with intermittent claudication (6% in Italy and 69% in Russia) and endovascular techniques (24% in Russia and 88% in Italy) [2]. Confirming these previous studies, one third of the current study cohort exhibited symptoms of a CLTI and 70% among all procedures included endovascular techniques.

Interestingly, in the current study, more than half of the cohort had a history of any lower extremity revascularisation, confirming previous reports using longitudinal data [18, 20]. This finding further emphasizes the importance to use patient-linked instead of rather procedure-related data since these redundant treatments would otherwise distort results derived from unlinked databases. However, to date, longitudinally linked multicentre registry data from Germany remains scarce. The RECCORD registry of the society for angiology enrolled 1000 patients with endovascular treatment of symptomatic PAD (25% with CLTI, 35% females, mean age 70 years) but the data collection primarily covered treatments performed by a single medical specialty [21]. In the current study, three different medical specialties were almost equally involved in the endovascular procedures, emphasizing the importance to include all specialties in data collections on endovascular treatments. Against that backdrop it appears noteworthy to highlight that all valid practice guidelines recommend a multidisciplinary approach but there is evidence suggesting an insufficient adherence concerning multidisciplinary team decisions in PAD treatment [22]. From 2013 through 2014, the German national registry for first line treatment strategies in patients with critical limb ischemia (CRITISCH register) collected multicentre data on 1200 patients suffering from CLTI from 27 selected centres. However, considering the current treatment reality and increasingly frequent invasive treatment of patients with intermittent claudication, it appears likewise important to cover the full spectrum of disease stages in real-world data [23].

Considering the ongoing COVID-19 pandemic, the unfavourable risk profile of the current study cohort deserves thoroughly reflection. More and more studies report a growing number of predictors for a severe illness. Males, octogenarians, patients with cardiovascular disease, diabetes, chronic liver and renal disease, chronic pulmonary disease, malignancy, and those with obesity and smoking are at higher risk when compared to the healthy population [24]. Notably, the current study included a highly vulnerable cohort affected by almost all of these severe comorbidities. It may be reasonable to focus on tertiary prevention and re-evaluate vaccination strategies to protect this central target population.

Against that backdrop, the fact that nearly half of the study cohort reported active smoking at the time being selected for invasive revascularisation appears striking. The central importance of smoking cessation was not only highlighted in all valid practice guidelines but is commonly accepted to be one of the most important drivers of early mortality in numerous global cohorts [3, 4, 5, 25, 26]. Together with the high proportion of obese patients in the current study, the modifiable risk factors may need more attention by the vascular community.

Limitations

Besides many strengths, there are also limitations. First, the patient selection and choice of treatment approach was left to the discretion of the physicians. This prospective observational study collected routinely collected data, and the non-random assignment makes it impossible to derive a causal relationship between treatment strategy and outcomes. Second, the study comprises 31 high-volume centres of about 650 hospitals providing vascular health benefits to the target population in Germany. Therefore,

a selection bias cannot be ruled out although centres with a large variety of characteristics from all over Germany were involved.

The GermanVasc data collection will be used for comprehensive outcome research during the following years. With a follow-up of one year and beyond, a meaningful comparison of commonly accepted quality indicators and objective performance goals is planned. The peculiar risk profile of this vulnerable cohort and its interaction with the intervention-outcome relationship will be further evaluated. The impact of renal insufficiency, cardiac comorbidities, female sex, and diabetes is of special interest. In the beginning of 2021, a medical device module was implemented to the registry platform in order to collect unique device identifiers (UDI) for the evaluation of long-term outcomes (www.mdepinet.de).

Conclusions

This study reports baseline characteristics from a large validated all-comer prospective cohort in Germany. The cohort covers a broader range of disease severity and types of interventions than usually found in trials. In future studies, the relation between treatment at baseline and outcomes will be analysed in more detail.

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Conflict of interest
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ORCID
Christian-Alexander Behrendt
https://orcid.org/0000-0003-0406-3319

Correspondence address
Assoc. Prof. Dr. Christian-Alexander Behrendt
Research Group GermanVasc
University Medical Center Hamburg-Eppendorf
Martinistraße 52
20246 Hamburg
Germany

behrendt@hamburg.de

Original communication

Prognostic interaction between age and sex on outcomes following carotid endarterectomy

Mario D'Oria[1], Barbara Ziani[1], Marco Damiano Pipitone[2], Paolo Manganotti[3], Roberta Pozzi Mucelli[4], Filippo Gorgatti[1], Francesco Riccitelli[1], Francesca Zamolo[1], Maurizio Fisicaro[5], and Sandro Lepidi[1]

[1] Division of Vascular and Endovascular Surgery, Cardiovascular Department, Cattinara University Hospital ASUGI, Trieste, Italy
[2] Division of Vascular Surgery, Bolzano Regional Hospital, Bolzano, Italy
[3] Clinical Unit of Neurology, Department of Medicine Surgery and Health Sciences, Cattinara University Hospital ASUGI, Trieste, Italy
[4] Radiology Unit, Department of Medicine Surgery and Health Sciences, Cattinara University Hospital ASUGI, Trieste, Italy
[5] Cardiovascular Health Services Centre, Cardiovascular Department, Maggiore Hospital ASUGI, Trieste, Italy

Summary: *Background:* The aim of this study was to assess the prognostic interaction between age and sex on peri-operative and follow-up outcomes following elective carotid endarterectomy (CEA) for asymptomatic and symptomatic carotid stenosis. *Patients and methods:* A retrospective review of all patients admitted to a single vascular unit who underwent elective CEA between January, 2015 and December, 2019 was performed. The primary endpoints of the study were overall survival (from index operation) and cumulative stroke rate at thirty days. *Results:* A total of 383 consecutive patients were included in this study; of these 254 (66.4%) were males. At baseline, males were younger (mean age 73.4±11 vs. 76.3±10 years, p=.01) and with lower proportion of octogenarians (20.4% vs. 28.7%, p=.05). The rate of stroke in symptomatic and asymptomatic patients (males vs. females) were as follows: a) whole cohort 1.9% vs. 2% (p=1.00) and 2.7% vs. 1.3% (p=.66), respectively; b) ≥80 years old 3.7% vs. 0% (p=1.00) and 4% vs. 5.9% (p=1.00), respectively; c) <80 years old 1.2% vs. 3.3% (p=.47) and 2.5% vs. 0% (p=.55), respectively. The 3-year survival estimates were significantly lower for males (84% vs. 92%, p=.03). After stratification by age groups, males maintained inferior survival rates in the strata aged <80 years (85% vs. 97%, p=.005), while no differences were seen in the strata aged ≥80 years (82% vs. 79%, p=.92). Using multivariate Cox proportional hazards, age (HR: 2.1, 95% CI: 1.29–3.3, p=.002) and male gender (HR: 2.5, 95% CI: 1.16–5.5, p=.02) were associated with increased hazards of all-cause mortality. *Conclusions:* In this study of elective CEA for asymptomatic and symptomatic carotid stenosis, similar peri-operative neurologic outcomes were found in both males and females irrespective of age. Despite being usually older, females have superior long-term survival rates.

Keywords: Carotid endarterectomy, carotid stenosis, gender, age, outcomes, stroke, survival, cardiovascular

Introduction

Although carotid endarterectomy (CEA) remains one of the most commonly performed vascular operations, as suggested by current clinical practice guidelines for the treatment of both symptomatic and asymptomatic carotid stenosis [1], with an excellent profile of early and late neurologic outcomes [2, 3], it still continues to attract considerable debate regarding optimal patient selection to achieve satisfactory peri-operative results as well as sustained long-term benefits. Age and gender, which represent the two strongest non-modifiable risk factors for vascular surgical outputs [4], have both been linked to variations in outcomes following CEA [5, 6]. However, their combined effect is still underreported.

The aim of this study was to assess the prognostic interaction between age and sex on peri-operative and follow-up outcomes following elective CEA for asymptomatic and symptomatic carotid stenosis. We hypothesized that the impact of age on outcomes after elective CEA would differ between male and female patients.

Patients and methods

Data collection

A retrospective review of all patients admitted to the Vascular and Endovascular Surgery Division of Trieste University Hospital who underwent elective CEA between

January, 2015 and December, 2019 was performed. The unit is the only facility offering specialized vascular care in the area, thereby making local referral patterns almost exclusive.

Patients with both asymptomatic ≥70% and symptomatic ≥50% carotid stenosis were enrolled. The grade of stenosis was defined based on duplex ultrasound (DUS) with the North American Symptomatic Carotid Endarterectomy Trial method [7, 8]; a subsequent computed tomography angiogram of the supra-aortic and intracranial vessels was performed to corroborate DUS findings. The definition of asymptomatic was based on current clinical practice guidelines (no previous neurologic symptoms or no neurologic symptoms in the preceding 6 months) [1]. Patients with hemodynamically significant contralateral carotid stenosis or contralateral carotid occlusion were not excluded. Patients affected by carotid aneurysms or dissections, carotid body tumors, restenosis after prior carotid interventions, or CEA performed in association with other surgical procedures including coronary artery bypass grafting (CABG) and common carotid artery stenting at its origin from the arch were excluded. Patients undergoing urgent/emergent CEA within 24 hours from onset of neurologic symptoms were also excluded.

Demographic baseline characteristics, cardiovascular risk factors, preoperative medical therapy, symptoms status, operative details, and in-hospital outcomes were obtained by reviewing all available medical records at the time of operation. Any other new clinical or neurological findings after discharge and within thirty days were assessed with telephone interviews at thirty days by a dedicated doctor according to our institutional protocols.

Any acute episode requiring urgent/emergency hospitalization, as well as vital status and death information, were assessed using the Trieste University Hospital Area Intranet System (which allows for visualization of medical records of all Trieste area hospitals and outpatients clinics). If death occurred outside Trieste Area, death certificates were retrieved as permissible by the vital records statutes within the region in which the decedent passed away. A patient was considered lost to follow-up when available clinical data were older than two years, but death could not be confirmed.

An institutional review board is not available in our institution and ethical approval was not necessary in view of the retrospective nature of the study design. Local departmental structures approved the study which did not alter standard care delivered to patients. All procedures performed in studies involving human participants were in accordance with the Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent for clinical research was obtained from all participants involved in the study at time of index operation.

Surgical practice

At our institution, CEA is always considered as the first-line treatment for both asymptomatic and symptomatic carotid stenosis unless specific contraindications exist (previous neck surgery/radiation, contralateral laryngeal nerve palsy, high carotid bifurcation).

All CEA procedures were performed by experienced vascular surgeons (≥15 procedures/year). Our surgical protocol has been described in prior publications [9]. Briefly, two methods of CEA were considered: standard CEA with longitudinal arteriotomy of the carotid bulb and internal carotid artery (ICA) origin followed by patch or direct closure (for a straight ICA), or eversion CEA with ICA resection at the carotid bulb and its re-implantation (for an ICA with kinking or redundant coiling). Polypropilene 6.0 suture was used for all vascular anastomoses. All surgical procedures were performed under general anesthesia with neurological monitoring achieved through continuous electroencephalographic (EEG) monitoring, with selective shunt placement in case of acute deterioration of EEG waves compared to preoperative baseline measurement.

Technical success was defined as an uneventful CEA without the need for additional procedures during surgery or on waking (defined as any unplanned surgical or endovascular maneuver that was prompted by clinical or imaging evidence of technical defects or neurologic symptoms). Completion angiography was not routinely performed unless deemed necessary by the surgeon performing the operation on a case-by-case basis.

Study endpoints

The primary endpoints of the study were overall survival (from index operation) and cumulative stroke rate at thirty days. Secondary endpoints included thirty-day composite of stroke/death/myocardial infarction, post-operative local complications (bleeding requiring reoperation and peripheral nerve palsy), and major adverse cardiovascular events (MACE) during follow-up.

Stroke was defined according to the current reporting standards [10]. The National Institute of Health Stroke Scale (NIHSS) was used for preoperative neurological assessment, at patient awakening, as well as at 6 and 24 hours after the procedure by a dedicated physician. A score of ≤4 represents a minor stroke, 5 to 15 a moderate stroke, 15 to 20 a moderate-severe stroke, and 21 to 42 a severe stroke (http://www.nihstrokescale.org/). In case of altered NIHSS as compared with baseline, the patient was subsequently and independently evaluated by a neurologist for accurate evaluation and management strategy. MACE were defined as the composite of any of the following: cardiovascular death, fatal or non-fatal MI, unplanned coronary revascularization, and congestive heart failure (CHF) requiring new or recurrent hospitalization.

Statistical analysis

All data were evaluated for normality with quantile-quantile plots. Continuous variables are expressed with mean±standard deviation. Categorical variables are presented as absolute numbers and percentage. Univariable

analyses were carried out with either Student's T test or Mann-Whitney U test for continuous variables, and chi-square test or Fisher's exact test for categorical variables.

Time-dependent outcomes were reported using life tables and presented as Kaplan-Meier curves with standard error <10%; differences were determined by the log-rank test. The estimates of the cumulative incidence of MACE and death were demonstrated using a competing-risk subdistribution model with MACE and death as mutual competing risks. Survival estimates were presented with 95% confidence intervals (CI).

Multivariable Cox Proportional Hazards was used to assess independent predictors for all-cause mortality and MACE, with results reported as hazard ratio (HR) with 95% CI:. Covariates for these models were selected based on previously described risk factors and univariate screen of all available potential confounders and backwards selection with a criteria of 0.25 to stay in the final models; these were tested for violation of proportional hazards assumptions using Schoenfeld residuals.

To account for the potential confounding of events occurring within the first year after index CEA, sensitivity analysis with evaluation of Kaplan-Meier estimates and Cox Proportional Hazards in the restricted cohort of patients free from any adverse event (mortality and/or MACE) through the initial 12 months following index operation. Results from the sensitivity analysis confirmed the original models in all instances analyzed (data not showed).

Statistical significance was set at alpha level of 0.05. No outcome data were missing. No imputation was used to address missingness predictors variables and only covariates with missing rate <1% were used in multivariable models; therefore, the only variables excluded from the final models were body mass index and baseline hemoglobin values. All statistical analyses were conducted using R language for statistical computing software and figures were produced using the package ggplot2.

Results

Study population

A total of 383 consecutive patients were included in this study; of these 254 (66.4%) were males and 129 (33.6%) were females. At baseline, males were younger (mean age 73.4±11 vs. 76.3±10 years, p=.01) and with lower proportion of octogenarians (20.5% vs. 28.7%, p=.05) as compared with females. Also, history of past or active smoking was more frequent in males than in females, in the overall cohort as well as after stratification by age (Table I). No other major differences were found in risk factors and comorbidities between study groups but for the higher incidence of diabetes mellitus in males as compared with females (42.7% vs. 31.0%, p=.03); this difference was also significant in the subgroup of younger individuals (43.8% vs. 28.3%, p=.01) but not in those aged ≥80 years (38.5% vs. 37.8%, p=1.00).

Peri-operative outcomes

Details of CEA procedure revealed no major differences between study groups (Table II), although the total operation time that was significantly longer for males as compared with females in the whole cohort (75±29 vs. 75±26 minutes, p=.05) and in the subgroup of elderly individuals (75±24 vs. 65±35 minutes, p=.05), but not in those aged <80 years (75±29 vs. 75±20 minutes, p=.28).

Univariate analysis of thirty-day outcomes did not reveal any significant differences between genders, in the whole cohort as well as after stratification by age groups (Table III). The rate of stroke in symptomatic and asymptomatic patients (males vs. females) were as follows: a) whole cohort 1.9% vs. 2.0% (p=1.00) and 2.7% vs. 1.3% (p=.66), respectively; b) ≥80 years old 3.7% vs. 0% (p=1.00) and 4.0% vs. 5.9% (p=1.00), respectively; c) <80 years old 1.2% vs. 3.3% (p=.47) and 2.5% vs. 0% (p=.55), respectively. Out of eight peri-operative stroke events that were reported in the whole study population, five were classified as moderate-severe and three were classified as moderate according to the NIHSS scoring system.

No other differences were noted in the thirty-day rates of stroke/death and stroke/death/myocardial infarction as well as in the occurrence of post-operative local complications.

Overall survival

In the overall population, the 3-year survival estimates were significantly lower for males as compared with females (84% vs. 92%, p=.03; Figure 1). After stratification by age groups, males maintained inferior survival rates in the strata aged <80 years (85% vs. 97%, p=.005), while no differences were seen with females in the strata aged ≥80 years (82% vs. 79%, p=.92). Using multivariate Cox proportional hazards, age (HR: 2.1, 95% CI: 1.29–3.3, p=.002) and male gender (HR: 2.5, 95% CI: 1.16–5.5, p=.02) were associated with increased hazards of all-cause mortality (see electronic supplementary material [ESM] 1).

Major adverse cardiovascular events

No significant differences were seen between males and females, in the whole cohort as well as after age stratification, in freedom from MACE at 3 years (males: 81% vs. females 90%, p=.142; Figure 2). The difference in estimates of freedom from MACE remained non-significant after age stratification. Using multivariate Cox proportional hazards, no independent predictors associated with MACE were found (ESM 2).

After accounting for the competing risk of death (Figure 3), the three-year risk for MACE in the whole cohort was 0.17 in males and 0.10 in females (p=.178). After stratification by age groups, the three-year risk of MACE was not significantly different in subjects aged ≥80 years (males: 0.19 vs. females: 0.16, p=0.701), but was significantly higher in males as compared with females in subjects aged <80 years (0.17 vs. 0.07, p=.015).

Table I. Baseline characteristics

Variables (Mean/SD) or (Number/%)	Overall population (Males, Females)	P value	≥80 years old (Males, Females)	P value	<80 years old (Males, Females)	P value
Mean age	73.7 (11.2)	**0.01**	82.5 (2.7)	0.41	71.3 (9.4)	0.06
	76.3 (10.3)		82.9 (2.8)		72.9 (8.2)	
Age ≥80	52 (20.5)	**0.05**	NA*	NA*	NA*	NA*
	37 (28.7)					
Symptomatic	107 (42.1)	0.51	27 (51.9)	1.00	80 (39.6)	0.25
	50 (38.8)		20 (54.1)		30 (32.6)	
Right side	129 (50.6)	0.91	28 (53.8)	0.67	101 (49.8)	0.90
	67 (51.6)		22 (59.5)		45 (48.4)	
BMI	26.2 (4.6)	0.94	25.5 (3.3)	0.98	26.3 (4.7)	0.80
	26.5 (4.9)		26 (5.6)		26.6 (4.8)	
Obesity (BMI 30 or more)	36 (18.5)	0.64	4 (10.0)	0.71	32 (20.6)	0.61
	21 (21.0)		4 (14.3)		17 (23.6)	
Smoking		**.001**		**0.05**		**0.05**
Past	84 (53.8)		13 (52.0)		71 (54.2)	
	31 (39.7)		7 (35.0)		24 (41.4)	
	49 (31.4)		7 (28.0)		42 (31.0)	
Active	20 (25.6)		2 (10.0)		18 (31.0)	
Hypertension	216 (85.0)	0.31	46 (88.5)	0.37	170 (84.2)	0.41
	104 (80.6)		30 (81.1)		74 (80.4)	
DM	109 (42.7)	**0.03**	20 (38.5)	1.00	89 (43.8)	**0.01**
	40 (31.0)		14 (37.8)		26 (28.3)	
History of CAD	59 (23.2)	0.90	12 (23.0)	0.34	47 (23.3)	0.65
	31 (24.2)		12 (33.3)		19 (20.7)	
Previous PCI/CABG	39 (15.4)	1.00	8 (15.4)	0.41	31 (15.3)	0.48
	20 (15.5)		9 (24.3)		11 (12.0)	
CHF	16 (6.3)	0.67	5 (9.6)	1.00	11 (5.4)	0.79
	10 (7.8)		4 (10.8)		6 (6.5)	
Atrial fibrillation	29 (11.4)	0.60	11 (21.2)	0.41	18 (8.9)	0.82
	12 (9.3)		5 (13.5)		7 (7.6)	
COPD	33 (12.9)	0.62	6 (11.5)	0.54	27 (13.3)	0.33
	14 (10.9)		6 (16.2)		8 (8.7)*	
CKD stage 3–5 (eGFR <60)	31 (12.2)	0.07	10 (19.2)	0.11	21 (10.4)	0.38
	8 (6.2)		2 (5.4)		6 (6.5)	
Symptomatic PAD	43 (16.9)	0.23	8 (15.4)	0.35	35 (17.2)	0.40
	15 (11.6)		3 (8.1)		12 (13.0)	
History of cancer	36 (14.1)	0.19	5 (9.6)	0.23	31 (15.3)	0.40
	25 (19.4)		7 (18.9)		18 (19.6)	
Baseline HB	13.8 (2.1)	**0.01**	13.1 (2.3)	0.35	14.05 (1.9)	**0.01**
	13.1 (2.1)		13.0 (2.4)		13.1 (1.9)	
Preoperative anemia (HB<13 in males or <12 in females)	78 (31.1)	0.29	24 (46.2)	0.13	54 (27.1)	0.67
	33 (25.6)		11 (29.7)		22 (23.9)	
Aspirin	214 (84.3)	1.00	41 (78.8)	0.26	173 (85.6)	0.49
	109 (84.5)		33 (89.2)		76 (82.6)	
Dual antiplatelet	34 (13.4)	0.75	6 (11.5)	0.37	28 (13.9)	0.25
	15 (11.6)		7 (18.9)		8 (8.7)	
Chronic anticoagulant	29 (11.5)	0.73	12 (23.1)	0.09	17 (8.5)	0.52
	13 (10.1)		3 (8.1)		10 (10.9)	
Statin	214 (84.6)	1.00	45 (88.2)	0.55	169 (83.7)	0.73
	110 (85.3)		31 (83.8)		79 (85.9)	
Diuretics	82 (32.2)	0.36	18 (34.6)	0.66	64 (31.5)	0.50
	48 (37.2)		15 (40.5)		33 (35.9)	
CCB/BB	159 (62.6)	0.91	34 (65.4)	0.82	125 (62.1)	1.00
	80 (62.0)		23 (62.2)		57 (62.0)	

(Continued on next page)

Table I. (Continued)

Variables (Mean/SD) or (Number/%)	Overall population (Males, Females)	P value	≥80 years old (Males, Females)	P value	<80 years old (Males, Females)	P value
ACEi/ARB	174 (68.6) 85 (65.9)	0.64	32 (61.5) 28 (75.7)	0.18	142 (70.4) 57 (62.0)	0.18

BMI: body mass index; DM: diabetes mellitus; CAD: coronary artery disease; PCI/CABG: percutaneous coronary intervention/coronary artery bypass grafting; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; PAD: peripheral artery disease; HB: hemoglobin; CCB/BB: calcium channel blockers/beta blockers; ACEi/ARB: angiotensin converting enzyme inhibitors/angiotensin receptor blockers. Bold numbers indicate significant p values (i.e. <.05).

Table II. Procedural details

Variables (Mean/SD) or (Number/%)	Overall population (Males, Females)	P value	≥80 years old (Males, Females)	P value	<80 years old (Males, Females)	P value
Ipsilateral ICA stenosis >70%	205 (85.4) 100 (83.3)	0.64	41 (83.7) 27 (77.1)	0.57	164 (85.9) 73 (85.9)	1.00
Ipsilateral CCA stenosis >70%	7 (3.1) 0 (0)	0.10	3 (6.2) 0 (0)	0.26	4 (2.2) 0 (0)	0.32
Contralateral ICA stenosis >70%	42 (19.6) 22 (19.3)	1.00	15 (32.6) 6 (18.8)	0.20	27 (16.1) 16 (19.5)	0.59
Contralateral CCA stenosis >70%	5 (2.4) 2 (1.8)	1.00	3 (6.4) 1 (3)	0.64	2 (1.2) 1 (1.3)	1.00
Bilaterally patent VA	146 (82.5) 74 (90.2)	0.18	30 (85.7) 17 (85)	0.86	116 (81.7) 57 (91.9)	0.16
Shunt	22 (8.6) 10 (7.8)	0.85	8 (15.4) 4 (10.8)	0.75	14(6.9) 6 (6.5)	1.00
Operation time (minutes)	75 (29.2) 75 (26.0)	0.06	75 (24.2) 65 (35.0)	0.06	75 (29.2) 75 (20.0)	0.30
Clamp time (minutes)	22 (11.0) 20 (9.5)	0.06	21 (14.5) 18 (12.0)	0.20	22 (11.0) 20 (9.0)	0.24
Eversion CEA	37 (14.5) 26 (20.2)	0.31	11 (21.2) 9 (24.3)	0.47	26 (12.8) 17 (18.5)	0.44

CCA: common carotid artery; ICA: internal carotid artery; VA: vertebral artery; EEG: electroencephalogram; CEA: carotid endarterectomoy.

Discussion

Atherosclerosis of the supra-aortic vessels and especially of the carotid bifurcation is a well-recognized cause of recurrent ischaemic stroke and there is evidence that stroke risk be related to the degree of carotid stenosis [11]. The CEA operation is widely acknowledged as the gold standard surgical approach for prevention of major cerebral events in patients with significant carotid stenosis, with landmark trials from the 1990s that favoured CEA plus best medical therapy (BMT) over BMT alone in the management of patients with significant carotid atherosclerotic disease [12, 13]. Both octogenarians and females were initially underrepresented categories in these major trials, while in real-world clinical practice both advanced age and female sex are not usually regarded as formal contraindications to carotid surgery. Furthermore, while isolated effects of age and gender on outcomes of CEA have been explored in previous studies [5, 6], their combined interaction remains almost unexplored. In that sense, the main novelty of our study is represented by the analysis of the combined prognostic effect that age and gender (which remain the two most important non-modifiable risk factors for surgical interventions) may have on peri-operative and follow-up outcomes, including survival and MACE, after CEA in a large contemporary real-world cohort of patients with symptomatic and asymptomatic carotid stenosis.

In our study, we found that males and females undergoing elective CEA for asymptomatic and symptomatic carotid stenosis share almost comparable distribution of cardiovascular risk factors irrespective of age. However, females were generally older with a mean age of 76 years (vs 73 years in males), and a higher proportion of females were octogenarians with almost 29% being aged ≥80 years (vs 20% in males). Despite these dissimilarities, we were unable to find any significant differences in the overall risk of adverse peri-operative neurologic events. These data demonstrate that perioperative risks are similar for males and females, and that sex should not be a factor when candidacy for CEA is sought in both asymptomatic and symptomatic patients. Nevertheless, our study highlighted that males undergoing CEA had lower long-term survival

Table III. Thirty-day outcomes

Variables (Mean/SD) or (Number/%)	Overall population (Males, Females)	P value	≥80 years old (Males, Females)	P value	<80 years old (Males, Females)	P value
Stroke						
Overall	6 (2.4)	0.72	2 (3.8)	1.00	4 (2.0)	1.00
	2 (1.6)		1 (2.7)		1 (1.1)	
Symptomatic	2 (1.9)	1.00	1 (3.7)	1.00	1 (1.2)	0.47
	1 (2.0)		0 (0)		1 (3.3)	
Asymptomatic	4 (2.7)	0.66	1 (4.0)	1.00	3 (2.5)	0.55
	1 (1.3)		1 (5.9)		0 (0)	
Stroke/Death						
Overall	6 (2.4)	0.72	2 (3.8)	1.00	4 (2.0)	1.00
	2 (1.6)		1 (2.7)		1 (1.1)	
Symptomatic	2 (1.9)	1.00	1 (3.7)	1.00	1 (1.2)	0.47
	1 (2.0)		0 (0)		1 (3.3)	
Asymptomatic	4 (2.7)	0.66	1 (5.9)	1.00	3 (2.5)	0.55
	1 (1.3)		1 (4.0)		0 (0)	
Stroke/Death/MI						
Overall	6 (2.4)	1.00	2 (3.8)	1.00	4 (2.0)	1.00
	3 (2.3)		1 (2.7)		2 (2.2)	
Symptomatic	2 (1.9)	1.00	1 (3.7)	1.00	1 (1.2)	0.47
	1 (2.0)		0 (0)		1 (3.3)	
Asymptomatic	4 (2.7)	1.00	1 (5.9)	1.00	3 (2.5)	1.00
	2 (2.5)		1 (4.0)		1 (1.6)	
Return to OR for bleeding	11 (4.3)	0.07	5 (9.6)	0.07	6 (3.0)	0.44
	1 (0.8)		0 (0)		1 (1.1)	
Peripheral nerve palsy	34 (13.3)	0.41	8 (15.4)	0.35	26 (12.8)	0.70
	13 (10.1)		3 (8.1)		10 (10.9)	
Hospital LoS (days)	3 (1.0)	0.95	3 (1.0)	0.72	3 (1.0)	0.73
	3 (1.0)		3 (1.0)		3 (1.0)	

MI: myocardial infarction; OR: operating room; LoS: length of stay.

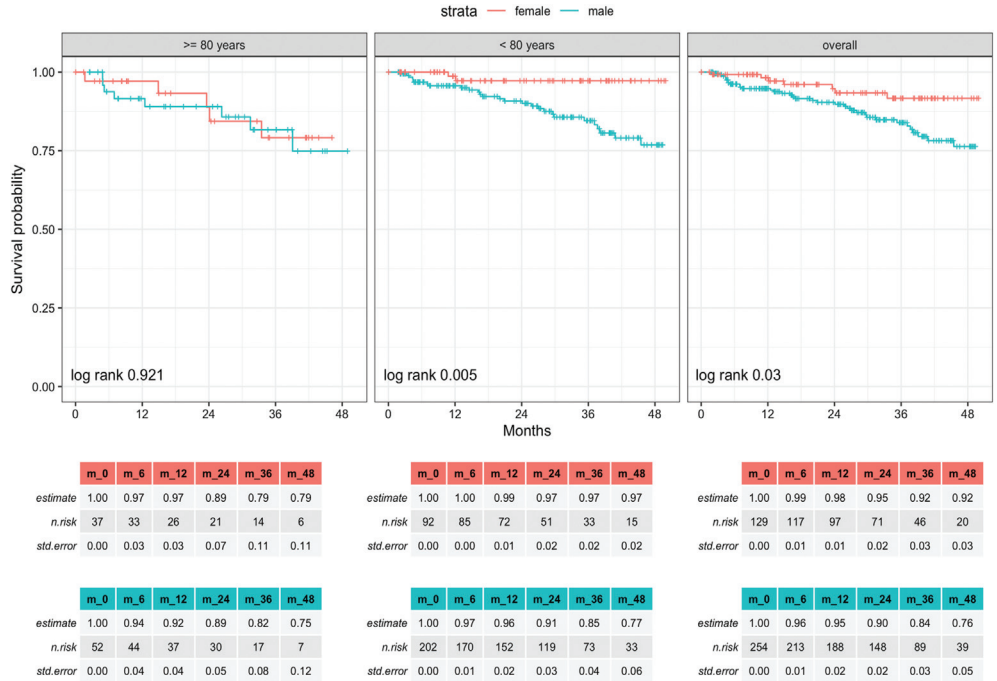
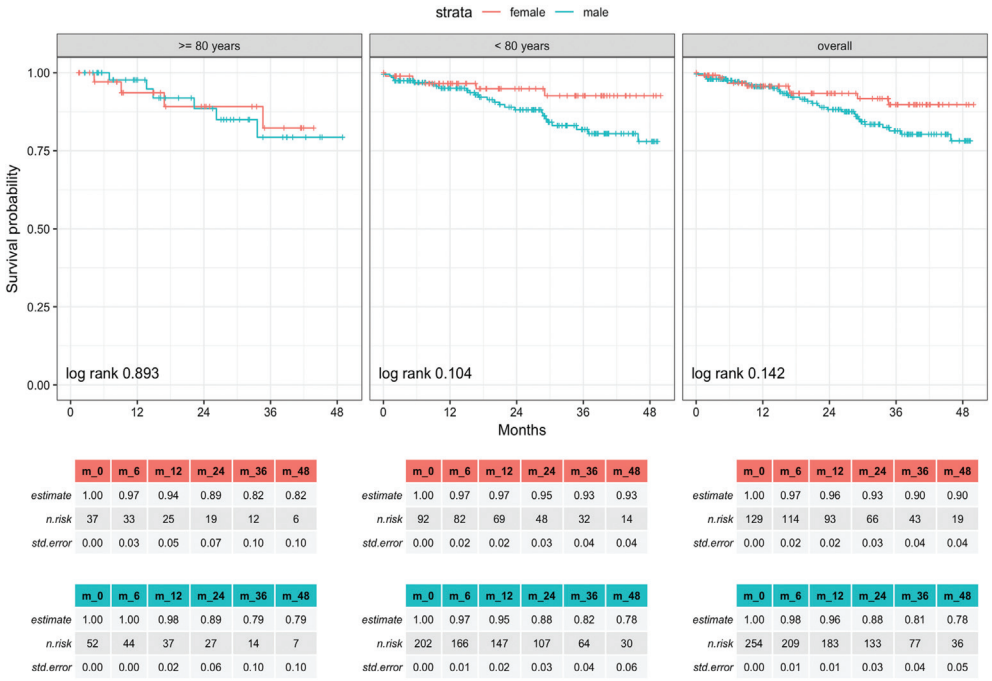


Figure 1. Kaplan Meier estimates of overall survival (males vs. females). Left box: age 80 years or more; middle box: age less than 80 years; right box: whole study cohort.



	m_0	m_6	m_12	m_24	m_36	m_48
estimate	1.00	0.97	0.94	0.89	0.82	0.82
n.risk	37	33	25	19	12	6
std.error	0.00	0.03	0.05	0.07	0.10	0.10

	m_0	m_6	m_12	m_24	m_36	m_48
estimate	1.00	0.97	0.97	0.95	0.93	0.93
n.risk	92	82	69	48	32	14
std.error	0.00	0.02	0.02	0.03	0.04	0.04

	m_0	m_6	m_12	m_24	m_36	m_48
estimate	1.00	0.97	0.96	0.93	0.90	0.90
n.risk	129	114	93	66	43	19
std.error	0.00	0.02	0.02	0.03	0.04	0.04

	m_0	m_6	m_12	m_24	m_36	m_48
estimate	1.00	1.00	0.98	0.89	0.79	0.79
n.risk	52	44	37	27	14	7
std.error	0.00	0.00	0.02	0.06	0.10	0.10

	m_0	m_6	m_12	m_24	m_36	m_48
estimate	1.00	0.97	0.95	0.88	0.82	0.78
n.risk	202	166	147	107	64	30
std.error	0.00	0.01	0.02	0.03	0.04	0.06

	m_0	m_6	m_12	m_24	m_36	m_48
estimate	1.00	0.98	0.96	0.88	0.81	0.78
n.risk	254	209	183	133	77	36
std.error	0.00	0.01	0.01	0.03	0.04	0.05

Figure 2. Kaplan Meier estimates of freedom from major adverse cardiovascular events (males vs. females). Left box: age 80 years or more; middle box: age less than 80 years; right box: whole study cohort.

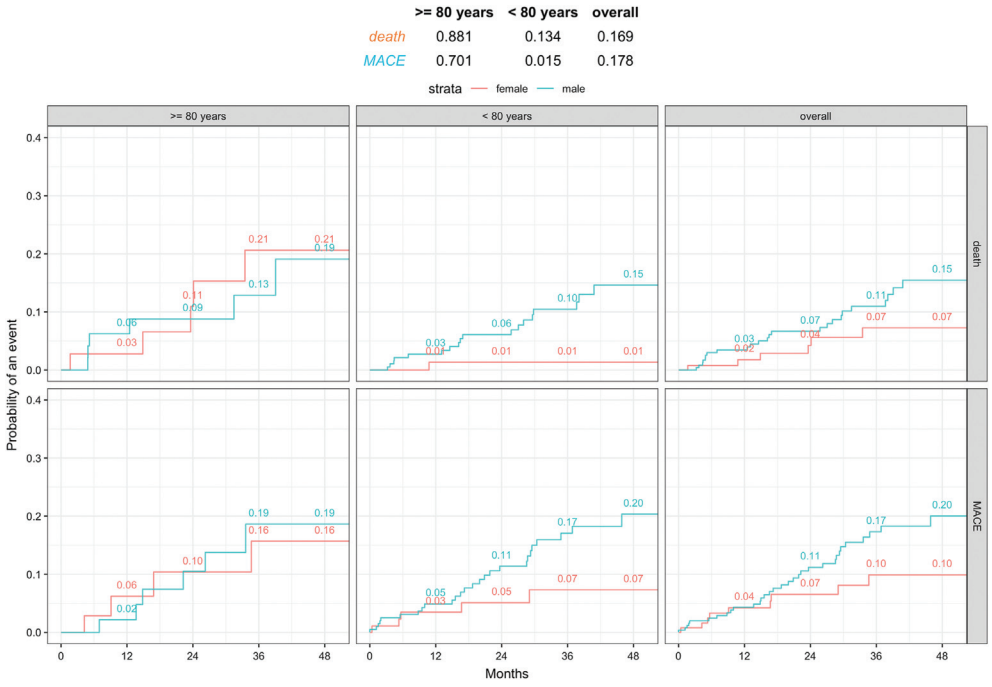


Figure 3. Cumulative incidence of mortality and major adverse cardiovascular events (MACE) with competing-risk subdistribution (males vs. females). Left box: age 80 years or more; middle box: age less than 80 years; right box: whole study cohort.

as compared with females, and the difference remained significant in those aged <80 years although survival rates were not significantly different in elderly individuals. Furthermore, multivariable analysis confirmed that age and male sex were both independently associated with higher odds of mortality, which may underline the presence of a combined age-gender effect on death risk in CEA patients.

Several factors may explain the higher risk of death in male patients following CEA, especially in non-octogenarians, when compared with females. Previous literature had already suggested that differences might exist in the pathophysiology of atherosclerosis owing to hormonal responses [14, 15]. In that sense, it might be hypothesized that elderly patients could share a similar long-term mortality risk due to accumulation of several comorbidities, while

in younger individuals the impact of cardiovascular disease (s) would play a major role, as suggested by the competing-risk analysis. The observation of more elderly females undergoing CEA in our study might also reflect less intensive cardiovascular screening in this specific population, which may merit further investigation. In fact, previous research has described that females are less likely to be diagnosed with coronary disease [16]; in turn, this may result in suboptimal management and contribute to an increase in mortality which, however, was not observed in the current study. Although this study cannot definitely support any of these arguments, it suggests that additional research is needed to determine what other factors may be driving this discrepancy between female and male patients.

Although no significant differences were found in the long-term rate of MACE between study groups, using a competing-risk subdistribution model we were able to find that risk of MACE was significantly higher for males as compared with females in subjects younger than 80 years. This observation, coupled with the lower long-term survival in this subset of patients, might indicate that cardiovascular events be the main driver of mortality. These findings may deserve further attention as they may be relevant to design patient-specific tailored approaches for follow-up and cardiovascular risk factors management. Interestingly, we did not find any significant differences in the medical management strategy between males and females although as many as 15% of study subjects were not on any statins at time of surgery. Therefore, medical optimization of patients undergoing CEA should be regarded as an unmet priority for cardiovascular specialists as well as primary care physicians.

Findings from this study must be interpreted in light of recommendations from current clinical practice guidelines, which recommend invasive treatment of carotid stenosis if reasonable life expectancy (5 years or more) can be anticipated [1]. The association between older age and increasing risk of mortality has already been described and the general concept that age predicts life expectancy still applies to this analysis. To date, only few scores have been proposed and have not become routine in clinical practice due to their limitations. Future studies should focus on external validation of existing score systems to predict mortality risk in CEA patients [17]. Therefore, the findings in the current study would provide further evidence that the treating physician should consider declining life expectancy with advancing age when making treatment recommendations to patients with carotid atherosclerotic disease.

However, age in itself should not be the sole criterion used for preoperative risk-stratification and risk scoring systems may be a valuable adjunctive tool for predicting long-term mortality. Indeed, recent research has focused on the impact of frailty on surgical outcomes. Frailty is defined as the accumulation of multisystem physiologic deficits that leads to decreased reserves and vulnerability to stressors, and that is known to increase the risk of adverse outcomes after surgery [18, 19]. The use of frailty index scores is based on the theory that the total accumulation of deficits, rather than the specific characterization of deficits that describe the phenotype, is an accurate descriptor of frailty [20]. Although frailty is a complex entity still difficult to assess in reproducible way, advanced age may be seen as a valid surrogate marker in many clinical instances [21]. On the basis of large epidemiologic studies, women tend to be more frail compared to men of similar age [22]. However, in the general geriatric population, they tend to live longer on average and may be able to tolerate frailty better, a phenomenon referred to as the sex frailty paradox [23]. How these considerations will apply to patients undergoing CEA may represent another area of future research endeavors.

Limitations

Findings from this study must be interpreted within the context of its limitations. First, this was a single-center retrospective study, thereby intrinsically prone to bias. Also, the number of males was almost twice as the number of females undergoing CEA in the study cohort. However, the relatively large sample size and long follow-up duration, coupled with the stability of surgical practice during the study timeframe, would make the results clinically reasonable. Furthermore, the recording of death events was highly accurate given the local referral patterns of treated patients. Indeed, the duration of follow-up was similar between males and females (mean 29.8 months, 95% CI: 27.6–32.0 vs. mean 28.6 months, 95% CI: 25.5–31.6; p=.43) as was the number of lost to follow-up (males: 8.7% vs. females: 4.7%; p=.21). Furthermore, retrieval of clinical data for the in-hospital phase was highly reliable, with no missing data on neurologic and mortality outcomes following CEA. Although we tried to account for significant confounders using robust multivariate analyses and confirmed the robustness of the main results with use of sensitivity analyses, it is still possible that some unmeasured confounders have remained.

Conclusions

In this study of elective CEA for asymptomatic and symptomatic carotid stenosis, similar peri-operative neurologic outcomes were found in both males and females irrespective of age. Despite being usually older, females have superior long-term survival rates. Cumulative risk of major adverse cardiovascular events during follow-up is higher in males than in females below 80 years of age.

Electronic supplementary material

The electronic supplementary material (ESM) is available with the online version of the article at https://doi.org/10.1024/0301-1526/a000957

ESM 1. Multivariate Cox Proportional Hazards for predictors of all-cause mortality [Figure].

ESM 2. Multivariate Cox Proportional Hazards for predictors of major adverse cardiovascular events (MACE) [Figure].

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ORCID
Mario D'Oria
https://orcid.org/0000-0002-7156-7827

Correspondence address
Dr Mario D'Oria
Division of Vascular and Endovascular Surgery
Cardiovascular Department
Cattinara University Hospital ASUGI
Strada di Fiume 447
34149 Trieste
Italy

mario.doria88@outlook.com

Original communication

An 18 year data-linkage study on the association between air pollution and acute limb ischaemia

Catherine A. Fitton[1], Bianca Cox[2], James D. Chalmers[1], and Jill J. F. Belch[1]

[1] University of Dundee NHS Tayside, Ninewells Hospital and Medical School, Dundee, UK
[2] Centre for Environmental Sciences, Hasselt University, Diepenbeek, Belgium

Summary: *Background:* There is limited information regarding the effects of air pollutants, such as nitrogen oxides (NO_x), nitric oxide (NO_2), nitrous oxide (NO) and particulate matter with a diameter smaller than 10 μm (PM10), on acute limb ischaemia (ALI), a peripheral arterial disease (PAD) often with a poor clinical outcome. *Patients and methods:* We conducted an 18-year retrospective cohort study using routinely collected healthcare records from Ninewells Hospital, Dundee, and Perth Royal Infirmary, in Tayside, Scotland, UK from 2000 to 2017. ALI hospitalisation events and deaths were linked to daily NO_x, NO_2, NO and PM10 levels extracted from publicly available data over this same time period. Distributed lag models were used to estimate risk ratios for ALI hospitalisation and for ALI mortality, adjusting for temperature, humidity, day of the week, month and public holiday. *Results:* 5,608 hospital admissions in 2,697 patients were identified over the study period (mean age 71.2 years, ±11.1). NO_x and NO were associated with an increase of ALI hospital admissions on days of exposure to pollutant (p=.018), while PM10 was associated with a cumulative (lag 0–9 days) increase (p=.027) of ALI hospital admissions in our study. There was no increase of ALI mortality associated with pollution levels. *Conclusions:* ALI hospital admissions were positively associated with ambient NO_x and NO on day of high measured pollution levels and a cumulative effect was seen with PM10.

Keywords: acute limb ischaemia, pollution, hospital admissions, death

Introduction

Globally, 8.8 million deaths and 85 million disability adjusted life years (DALYs) a year are associated with air pollution [1]. While pollution related illnesses are often linked with middle- and low-income countries, pollution remains an important factor in developed countries, with around 40,000 deaths/annum in the UK [2]. Air pollution has been linked to a range of conditions [3], such as: cancer, asthma, exacerbations of bronchiectasis, stroke, heart disease, diabetes, and dementia.

Currently, limits on air pollution in Scotland are set by the Scottish government, using the World Health Organization's (WHO) air quality guidelines [1]. While the WHO documents give so-called "safe levels", it is recognised that they are unlikely to be entirely safe for the whole population [4]. In Scotland, limits of 40 $\mu g/m^3$ for nitrogen dioxide (NO_2), 30 $\mu g/m^3$ for nitrogen oxide (NO) and 18 $\mu g/m^3$ for particulate matter with a diameter smaller than 10 μm (PM10), have been set, and low emission zones have been introduced to larger cities in an effort to decrease air pollution from traffic. Despite this, air pollution is frequently not appreciated by Councils, particularly in semi-rural towns where it is seen as a "big city" problem, and pollution limits are not enforced.

Acute limb ischaemia (ALI) is defined as a sudden decrease in lower limb perfusion [5] which can lead to extensive tissue necrosis unless treated urgently [6]. ALI affects 1–1.5 individuals per 10,000 per year [7], and causes can be broadly split into two groups: embolism and thrombosis, excluding trauma [5]. Air pollution has been linked previously with embolism [8, 9] and thrombosis [9, 10] in other arterial regions. Air pollution is thought to induce inflammation [11], which triggers ischaemic damage by arteriosclerosis or thrombosis [12, 13, 14, 15]. There is no literature regarding the effects of air pollution on the incidence of ALI, a disease which can have serious consequences for the patient, such as amputation and significant disability.

This study, from the Tayside Pollution Research Programme (TPRP), aimed to investigate the association of air pollution on ALI hospital admissions and deaths over an 18-year period, across Tayside, a semi-rural area of Scotland, containing two of Scotland's smaller cities:

Dundee (population circa 148,270) and Perth (population circa 44,820).

Materials and methods

This is a time series cohort study using data linkage. Exposure variable is pollutant (NO_x, NO_2, NO, PM10). Confounding variables are temperature, humidity, day of week, public holiday, month and year. Outcome variable is ALI admission

Consent for the study was given by the Tayside Caldicott Guardian. Ethics approval and patient consent were not required as this data linkage study did not include patient participation. All data storage and analyses were carried out on anonymised data, held within the Safe Haven, the Tayside Health Informatics Centre (HIC). Hospital data is available from HIC with appropriate permissions. Pollution data is publicly available from: https://uk-air.defra.gov.uk/data/data_selector.

Patient population and patient data linkage

This manuscript describes a record linkage study of hospital admissions at Ninewells Hospital, Dundee, UK and Perth Royal Infirmary, Perth, UK, from January 1st 2000 to December 31st 2017. These two hospitals are the catchment hospitals for ALI patients. Unique personal identifier codes (CHI) were used to extract electronic medical records from the Scottish Morbidity record 01 (SMR01) database that documents all hospitalization events in Scotland. Deaths were extracted from the National Records of Scotland (NRS) database.

Hospital admission and death definition

Hospital admissions and deaths of interest were agreed a priori and were defined by ICD10 code (2016 addition) recorded on the SMR01 or NRS records. Hospital admission for ALI or cause of death as ALI was defined as an IDC10 code of: I739: peripheral vascular disease, unspecified; I74: arterial embolism and thrombosis; or I702: atherosclerosis of arteries of extremities (full list of codes can be viewed in electronic supplementary material [ESM] 1). Only those with the appropriate ICD10 codes listed as a primary reason for hospital admission or death were included. Our vascular surgeons were consulted and confirmed that these ICD10 codes are used to capture "new onset acute limb ischemia within previous 24–48 hours with no past history of chronic critical limb ischemia". Hospital admissions and deaths were restricted to patients over 45 and were aggregated to provide daily total ALI admissions and death. Admissions were also restricted to only those who reside in Dundee and Perth, in the following postcode districts: DD1, DD2, DD3, DD4, DD5, DD6, DD7, PH1 and PH2.

Pollution data

Pollution information is measured daily at urban background sites, throughout the UK, as part of the UK's Automatic Urban and Rural Network (AURN). Daily NO_x, NO_2, NO and PM10 concentrations measured in Dundee and Perth were used for the analysis. Pollution data from Seagate was used for Dundee, while Atholl street was used for Perth. Data on mean air temperature and relative humidity were obtained from the UK Meteorological Office. Temperature and humidity data from Dalwhinnie were used for Perth, while temperature data from Mylnefield, near Dundee and humidity data from Leuchars, Fife was used for Dundee.

Supplemental figures 2, 3, 4 (ESM 2, 3, 4) show the measurement stations and postcode areas used. As pollution levels showed similar patterns and levels of pollution in each city, pollution levels were combined, and a daily average calculated and used for the analysis.

Where <23 data points were missing over a day, the rest of the points were averaged for the day. Where all data points were missing for the day, the day was excluded. The total number of excluded days was 4.

Statistical analysis

To account for delayed effects of air pollution on ALI admissions, we combined quasi-Poisson regression with distributed lag (non-linear) models (DL(N)M) [16, 17], using separate models for PM10, NO_x, NO_2 and NO. DL(N)Ms enable the investigation of the temporal pattern of the association, providing an estimate of the "overall" effect of the high measured pollution levels, incorporating potential delayed and harvesting effects. A DL(N)M model is defined through a "cross-basis" function, a bi-dimensional space of functions describing simultaneously the shape of the relationship along the space of the predictor (exposure-response function), and its distributed lag effects (lag-response function). We used a linear exposure-response function for the association between air pollution exposure and hospital admissions/deaths. The number of days included in the cross-basis was chosen based on visual inspection of the 3D exposure-lag-response surfaces. As exposure-response curves of all pollutants were relatively flat (i.e. risk ratios close to one) nine days after the high measured pollution levels, an extended lag period of 0–9 days (day of exposure up to 9 days after) was used. The lag structure was modelled with a natural cubic spline with two degrees of freedom (df), placing the knots at equally spaced values on the log scale of lags to allow more flexible lag effects at shorter delays [18]. Categorical variables for day of the week (1–7), month (1–12) and public holidays (0 or 1) were included in the model to control for any weekly or monthly patterns in ALI admission. To account for the (potentially delayed) effects of meteorological factors on ALI admissions [19], we also included DLNM cross-bases for mean temperature and for humidity in the model. In both cross-bases, the maximum lag was set to 14 days and natural cubic splines with

Table I. Pollution levels in Dundee and Perth over the study period

	All data					Dundee					Perth				
	Min	P25	Median	P75	Max	Min	P25	Median	P75	Max	Min	P25	Median	P75	Max
NO_x	16.1	109.0	146.0	190.0	570.0	11.3	120.4	165.0	210.4	713.0	18.1	94.5	134.0	182.0	615.0
NO_2	9.3	41.2	51.1	61.7	118.0	7.8	39.5	49.7	56.0	150.0	0.0	39.4	52.0	64.1	136.0
NO	4.5	44.2	61.8	84.7	294.0	1.7	51.9	75.0	98.2	367.0	5.4	34.9	52.9	76.9	323.0
PM10	2.9	12.5	16.8	22.8	89.5	1.0	9.2	13.4	19.5	93.6	1.0	15.8	21.0	27.5	105.0

Mean and median for the whole study period, and for 2017 only, and highest/lowest quartiles are given. Pollution is measured as $\mu g/m^3$. NO_x: nitrogen oxides; NO_2: nitric oxide; NO: nitrous oxide; PM10: particulate matter with a diameter smaller than 10 μm.

five df were used to model the exposure-response and the lag-response functions, respectively.

Risk ratios (RR) of hospital admissions and deaths were calculated for a 10 $\mu g/m^3$ increase in air pollutant concentrations. Reported estimates, computed as the risk at day 0 (day of high measured pollution levels), and the cumulative risk over the total lag period, are presented with corresponding 95% confidence intervals (CI).

In a next set of DL(N)M models, air pollution exposures were categorized into quartiles, and RRs of ALI admissions for high pollution days (fourth quartile) versus low pollution days (first quartile) were estimated. As there was little difference between pollution levels in Dundee and Perth, quartiles were calculated by using combined pollution data.

Potential reduction in ALI admissions were calculated, using mean total admissions. These estimates were used to calculate the potential reduction in ALI admissions for a reduction in air pollution concentrations from the fourth to the first quartile. The reduction was calculated relative to the mean number of admissions over the study period. Due to the small numbers of ALI related deaths during the study period (n=1003 deaths with ALI recorded as primary cause of death), potential reduction of deaths associated with pollution reduction were not calculated. All analyses were performed with the statistical software R (R Foundation for Statistical Computing, Vienna, Austria) using the "dlnm" package (https://cran.r-project.org/web/packages/dlnm/index.html).

Results

Over the 18-year study period, out of 5,608 admissions to hospital 2,697 people had a primary admission reasons of ALI, as defined in the methods. Of these, 4,280 admissions in 2,032 people were within Dundee, and 1,328 admissions in 665 people were from Perth. For the ICD10 codes of I702, I739 and I74, there was a total of 28, 2460 and 318 patients admitted to hospital over the study period, respectively (with 112 of these being admitted for more than one code). This accounted for 33, 5,181 and 394 admissions respectively. The average age of patients admitted for ALI was 71.2 years (SD=11.1 yrs). There were 1003 deaths where the primary cause of death was registered as ALI over the study period.

Pollutant levels of the study area and split for city are displayed in Table I. Quartiles were defined using joint data for Dundee and Perth.

ALI hospital admissions

Figure 1 shows lag-specific RRs for ALI hospitalization associated with a 10 $\mu g/m^3$ increase in air pollution concentrations. Increased ALI hospitalization was observed on the day (lag 0) and the day after (lag 1) the exposure for all pollutants. Same-day (lag 0) RRs for a 10 $\mu g/m^3$ increase in air pollutant concentrations were significant for NO_x (1.006; 95% CI 1.001–1.011)) and NO (1.012; 95% CI 1.002–1.022), but not for NO_2 (1.020; 95% CI 0.998–1.042)) and PM10 (1.018; 95% CI 0.991–1.046) (Table II). Corresponding cumulative (lag 0–9) estimates did not reach significance for any of the pollutants. RRs for high (fourth quartile) versus low (first quartile) air pollution concentrations on the day of exposure (lag 0) were statistically significant for all four pollutants: 1.185 (95% CI 1.072–1.309), 1.098 (95% CI 1.000–1.206), 1.203 (95% CI 1.089–1.330) and 1.068 (95% CI 0.990–1.152), for NO_x, NO_2, NO and PM10, respectively. Although day of high pollution did not produce significant results for PM10, corresponding cumulative (lag 0–9) estimate was significant for PM10 (RR=1.283; 95% CI 1.028–1.601), though the lag phase data were not significant for the others.

Reduction in ALI hospital admissions

There was an average of 320.5 ALI hospital admissions per year over the study period. If pollution levels were kept within the quartile 1 level of pollution for NO_x, NO_2, NO and PM10, we calculated that this would result in a potential 19–32% reduction in ALI admissions (Table III).

Mortality data

There was no association between any of the pollutants, NO_x, NO_2, NO and PM10 and an increased risk of ALI deaths during the study period, when assessing pollution as 10 $\mu g/m^3$ increments or as quartiles (ESM 5).

Discussion

This study assessed the relationship between NO_x, NO_2, NO and PM10, air pollution on ALI hospital admissions and deaths, in Tayside, Scotland. We report the novel finding in ALI that NO_x and NO were significantly associated

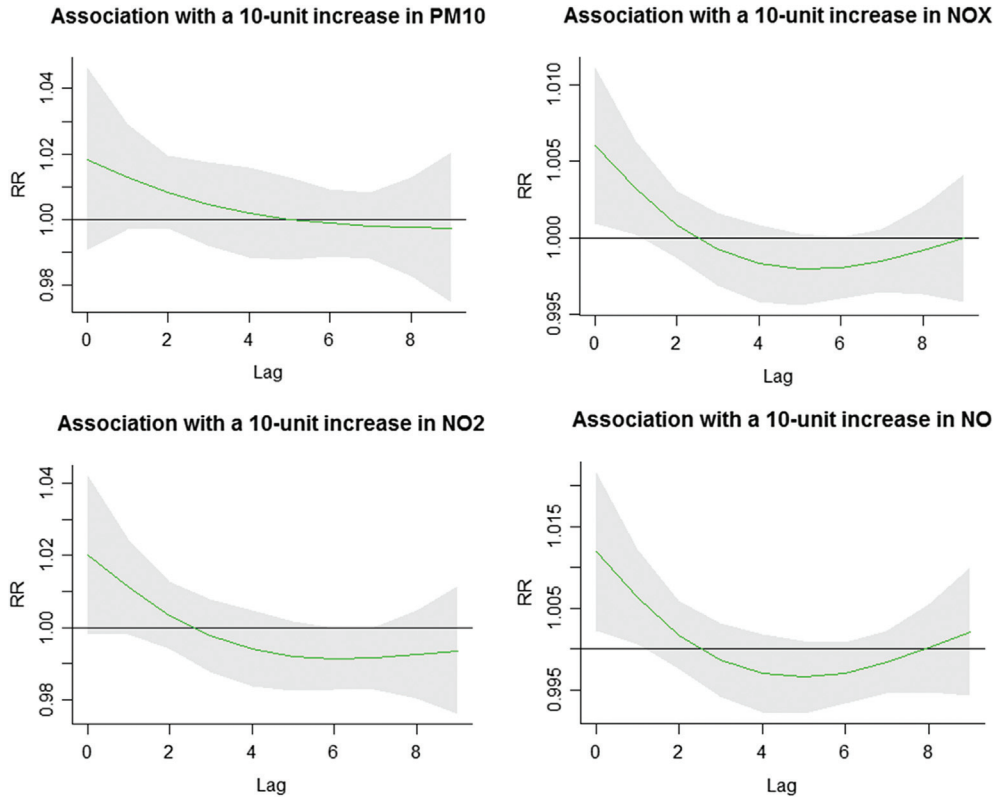

Figure 1. Slice diagrams demonstrating the risk ratio trend for acute limb ischaemia (ALI) hospital admissions over the lag period (0–9 days) for a 10 μg/m^3 increase in particulate matter with a diameter smaller than 10 μm (PM10), nitrogen oxides (NO_x), nitric oxide (NO_2), nitrous oxide (NO).

Table II. Adjusted risk ratios with 95% confidence intervals at day 0 and cumulative risks (0–9 days) for Acute Limb Ischaemia hospital admissions and exposure to 10 μg/m^3 increase in pollutants and quartile 4 vs quartile 1

	10 μg/m^3		Q4 vs Q1	
	RR (95% CI)	P value	RR (95% CI)	P value
Day 0				
PM10	1.018 (0.991–1.046)	0.197	1.068 (0.990–1.152)	0.089
NO_x	1.006 (1.001–1.011)	0.018	1.185 (1.072–1.309)	0.001
NO_2	1.020 (0.998–1.042)	0.072	1.098 (1.000–1.206)	0.050
NO	1.012 (1.002–1.022)	0.018	1.203 (1.089–1.330)	<0.001
Cumulative				
PM10	1.039 (0.965–1.119)	0.316	1.283 (1.028–1.601)	0.027
NO_x	1.001 (0.986–1.017)	0.907	1.148 (0.837–1.576)	0.400
NO_2	0.986 (0.924–1.053)	0.685	1.003 (0.747–1.346)	0.986
NO	1.010 (0.982–1.039)	0.499	1.138 (0.832–1.529)	0.412

Models adjusted for day of week, month, public holiday, daily temperature and humidity. NO_x: nitrogen oxides; NO_2: nitric oxide; NO: nitrous oxide; PM10: particulate matter with a diameter smaller than 10 μm.

with an increase of ALI hospital admissions on the day of exposure, with evidence of an effect throughout the lag period, which reached significance for PM10. There was no association between ALI deaths and high pollution levels.

There is some early work on air pollution and development of peripheral arterial disease in general [20, 21, 22] but no-one has evaluated the effect on ALI. Our study therefore adds a novel finding to the limited knowledge regarding the adverse effects of NO_x and NO air pollution, which is increasing Acute Limb Ischaemia events on high pollution days. As NO_x is a majority mixture of NO, NO_2 with other particulates, it is likely that the increased risk for NO_x is driven by the NO proportion in our study. We know that these gases, when inhaled, reach the blood stream where they have a noxious effect by directly damaging endothelium, increasing blood pressure and increasing the oxidation of LDL [23] and it is therefore unsurprising to see an immediate effect on the day of high gas levels.

PM10 pollution is arguably the most researched constituent of air pollution and has previously been linked with various adverse cardiovascular outcomes [24]. Exposure to

Table III. Potential reduction of acute limb ischaemia hospital admissions per year for each pollutant, if all days were within Q1 limits. Based on admission data from 2016/2017 in Dundee – based on a mean total admins/yr of 320.5

Pollutant	Mean reduction in admins/day	Mean total reduction/yr	% Reduction
NO_2	0.23	83.14	25.9
NO	0.29	105.57	32.9
NO_x	0.29	104.36	32.6
PM10	0.17	61.90	19.3

NO_x: nitrogen oxides; NO_2: nitric oxide; NO: nitrous oxide; PM10: particulate matter with a diameter smaller than 10 μm.

PM10 has been postulated to produce systemic inflammation, thrombotic reaction, and autonomic nervous system imbalance [25, 26, 27]. There is a large body of literature of how air pollution affects arteries, although most experimental work has been done on peripheral arteries, the papers use these experiments to extrapolate to coronary vessels and may also explain ALI. We report a significant association between the ALI hospitalisation and the cumulative effects of PM10. PM10 particles induce an inflammatory repose over time. Exposure to PM 10 is associated with elevated systemic levels of C-reactive protein (CRP), elevated blood viscosity and thrombus formation [28].

We also calculated that if pollutant levels were reduced to quartile 1 levels there is a potential to reduce ALI hospital admissions by 30%. However, we cannot say what the association is between each pollutant type.

Limitations

Some limitations of the study should be addressed: firstly, the study design does not take into account individual person factors (previous cardiovascular disease, smoking, diabetes), which may be associated with ALI admissions, or extent of exposure, although we did exclude the ICD10 codes for ALI secondary to diabetes which would have excluded all patients with known diabetes at the time of admission. It is unlikely that chronic risk factors are associated with short-term fluctuations in air pollution levels, however future welldesigned cohort studies taking into account key risk factors and comorbidities would be helpful to confirm the findings in this study.

Secondly, it is recognised that air pollution can promote arrythmia [29] and arrythmia is a common cause of ALI, when an embolus is thrown off from a fibrillating heart. We are unable to determine if this was the case, as we had no access to ECGs. If embolus were the cause this would make the ALI a secondary effect of the pollution, albeit a most serious one.

We also used single monitoring stations in Dundee and Perth to estimate personal exposure to air pollution, which may result in magnitude of effects on exposures to air pollution obtained from regression modelling to be smaller than the actual impact, due to non-systematic exposure misclassification [30]. Furthermore, as the pollutants are modelled separately, we cannot say whether they provide an additive effect. NO_x, NO_2 and NO are likely to be highly correlated. In addition to these limitations, ambient air pollution may not translate directly to population exposure.

Another limitation of this study is there is no way to determine whether use of ICD10 codes used to identify hospital admissions is consistent between hospitals or over time.

There has been a focus on improving air quality in the UK for the past 20 years, which has largely centred on the reduction of PM10 pollution. However, more needs to be done in Tayside, and elsewhere, where these results might be extrapolated, to address the high NO_x and NO pollution levels, particularly considering the increased risks reported here, and in other studies [11, 12, 13, 14, 15, 26].

Conclusions

We report for the first time a significant increase of acute limb ischaemia hospital admissions following high measured pollution levels of NO_x, NO and PM10 air pollution on day of exposure. If air pollution were kept to low levels, acute limb ischaemia hospital admissions in Tayside could be potentially reduced by 30%.

Electronic supplementary material

The electronic supplementary material (ESM) is available with the online version of the article at https://doi.org/10.1024/0301-1526/a000972

ESM 1. Table of ICD10 codes used over the study period and descriptions. ICD10 codes did not change through the updated versions of ICD10, and so these codes are valid for each reiteration (2000–2106) (Table)

ESM 2. Map of Scotland districts. Dundee city, Perth city, Milnfield and Leuchars stations are marked (Figure)

ESM 3. Dundee postcode districts, with city centre marked. DD1, DD2, DD3, DD4, DD5, DD6 and DD7 were used in this study (Figure)

ESM 4. Perth postcode districts with city centre marked. PH1 and PH2 used for this study (Figure)

ESM 5. Adjusted risk ratios with 95% confidence intervals at day 0 and cumulative risks (0–9 days) for acute limb ischemia deaths and exposure to 10 $\mu g/m^3$ increase in pollutants, and quartile 4 vs quartile 1 (Table)

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Conflict of interest
The authors declare that there are no conflicts of interest.

Author contributions
JJFB had the original concept. CAF, BC, JC, JJFB agreed on the project design. CAF undertook the analysis, CAF, BC, JC, JJFB interpreted the results. CAF drafted the manuscript and CAF, BC, JC, JJFB made changes and agreed on the final manuscript.

Correspondence address
Prof. Jill J. F. Belch
University of Dundee
Ninewells Hospital and Medical School
Dundee DD1 9SY
UK

j.j.f.belch@dundee.ac.uk

Original communication

First experiences of local pulse wave velocity measurements in 4D-MRI in focally stented femoropopliteal arteries

Ingo Hermann[1], Tetyana Shchetynska-Marinova[2], Klaus Amendt[2], Anna-Lena Hohneck[2], Stefan O. Schönberg[3], Frank G. Zöllner[1], and Martin Sigl[2]

[1] Computer Assisted Clinical Medicine, Mannheim Institute for Intelligent Systems in Medicine, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany
[2] First Department of Medicine, University Medical Centre Mannheim, Medical Faculty Mannheim, University of Heidelberg and DZHK (German Center for Cardiovascular Research) partner site Heidelberg/Mannheim, Mannheim, Germany
[3] Department of Clinical Radiology and Nuclear Medicine, University Medical Center Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

Summary: *Background:* In peripheral arterial disease (PAD) the femoropopliteal (FP) artery is the most frequently recanalized lower limb artery. Stent-based interventions change the biomechanical properties of FP arteries. However, no clinical tool for functional imaging is established for quantitative measurements in vivo. Four-dimensional-flow magnetic resonance imaging enables a detailed evaluation of the hemodynamics of the central and – more challenging – the peripheral arteries. The present study aimed to determine the feasibility of assessing pulse wave velocities (PWV) as a marker of vessel stiffness in PAD patients with multiple spot stents and to compare the values with age-matched subjects and young-adult healthy subjects. *Patients and methods:* Contrast-free 4D-flow MRI was performed in seven PAD patients with focally stented FP arteries, five age-matched subjects after exclusion of PAD, and five young, healthy adults. PWV values were calculated from flow curves by using the foot-to-foot method. *Results:* Four-D-flow MRI sequences offering high spatial and temporal resolution enables quantification of flow velocity measurements and estimation of PWVs. Assessment of segmental PWV as a surrogate of vascular stiffness in focally stented femoral arteries is feasible. PWV values across all groups were 15.6±5.2 m/s, 13.3±4.1 m/s, and 9.9±2.2 m/s in PAD patients, senior-aged volunteers, and young-adult volunteers respectively. PWV values in PAD patients were similar with those in the senior-aged volunteers group (15.6±5.2 vs. 13.3 ±4.1 years, p=0.43). However, when compared to the young-adult volunteers, PAD patients had a statistically significantly higher mean local PWV (15.6±5.2 m/s vs. 9.9±2.2 m/s, p<0.05). *Conclusions:* Calculating segmental PWV in the femoral arteries is feasible in PAD patients with focally stented FP arteries. PWV values in PAD patients were similar to those in senior-aged volunteers, both of which were higher than in young-adult volunteers.

Keywords: 4D-flow MRI, pulse wave velocity, femoropopliteal artery, stiffness

Introduction

Peripheral arterial disease (PAD) affects around 237 million people worldwide [1]. A stenosis or occlusion of the femoropopliteal (FP) artery is the most common lesion in intermittent claudication [2] and the FP artery is by far the most common recanalized lower limb artery [3]. According to the current guidelines, percutaneous intervention is the preferred first-line treatment modality for patients with symptomatic FP lesions [4, 5, 6, 7].

A special feature of the FP artery is the high deformation stress. When the limbs are moved, there is significant bending, shortening and twisting [8, 9]. The biomechanical forces on the FP artery are made largely responsible not only for the occurrence of degenerative vascular changes, but also for the failure of recanalizing therapies with and without stent deployment in middle- and long-term follow-up, in particular in long complex lesions [9, 10, 11, 12]. The incidence of restenoses after an initially successful vascular intervention is between 5% and 70% within one year, depending on endogenous and procedural factors [13]. In stent-based FP interventions, stents are deployed planned ("primary stenting") or as a "bailout", when elastic recoil and intimal dissection after balloon-dilation is managed with mechanical scaffolding in order to stabilize the vessel lumen. However, the mechanical properties of the metal scaffolds used are not identical to the biomechanical properties of the FP artery. In a perfused human

cadaver model, however, none of seven different stents was able to match all FP deformations without changing the deformations of the vessel inside or outside the stent [14]. The modern interventional strategy of implanting foreign bodies "as less as reasonably achievable" [15] aims to minimize traumatic interactions between the implant and the vascular wall, to avoid stent fractures and instent-restenosis and to enable bypass anastomoses on stent-free vessel segments, if necessary. The concept of "spot stenting" (SS) has demonstrated good clinical results in conceptual research [16], dedicated registries [17, 18] and a randomized-controlled trial [19] and favourable patency rates compared to the conventional "full-metal jacket" strategy [16, 19]. Although the results seem to be promising, the hemodynamic and biomechanical consequences of multiple short stents are unclear [20]. A better understanding of the dynamic environment of the FP artery is crucial to optimise treatment strategies in the future. SS opens up diagnostic options. While long-segment metallic stents can severely disturb diagnostic vascular imaging [21], SS significantly reduces metal burden leaving 38 – 60% of the total lesion length "stent-free" [16, 17, 19, 22]. In this study, we aimed to assess the feasibility of 4D-flow MRI of assessing the local PWV of the stented FP arteries.

Patients and methods

Study design and setting

This study was a prospective, single-center pilot study, conducted at the University Medical Centre Mannheim. Contrast-free 4D-flow MRI measurements were performed in PAD patients with focally stented FP arteries, age-matched subjects after exclusion of PAD and without known cardiovascular morbidities and young healthy adults.

PAD patient cohort

The patient group consisted of seven consecutive PAD patients after SS using the VascuFlex® Multi-LOC stent system (B.Braun Melsungen, Germany). The interventional procedures had been performed at the Diakonissenkrankenhaus Mannheim in Germany, a teaching hospital of the University of Heidelberg. All patients of the study cohort had initially been entered in the LOCOMOTIVE EXTENDED registry (Clinical-Trials.gov Identifier: NCT02900274) the data from which have been published previously [17]. Briefly, the VascuFlex® Multi-LOC system is a multiple stent system with six self-expanding Nitinol stents with a length of 13 mm each. Stents had been deployed as a bailout in case of insufficient acute results (flow limiting dissections or persisting stenosis>30%) following antegrade plain old angioplasty and/or drug coated balloon dilatation of symptomatic de novo FP lesions. Balloon and stent diameters were based on the reference lumen diameters, avoiding oversizing.

PAD eligibility criteria

In order to minimize 4D-flow MRI measurement errors associated with modifications in the featuring shape of pulse waveforms acquired from different arterial sites [23], the following eligibility criteria were defined: 1) Duplex sonographic exclusion of relevant steno-occlusive lesions in the (aorto-iliac) inflow and (popliteo-crural) outflow of the superficial femoral artery. 2) Biphasic flow profile waveform with fast systolic upstroke (acceleration time<100 ms; similar acceleration time in the proximal and distal superficial femoral artery) along the whole superficial femoral artery. 3) Crural two- or three-vessel run-off without high-grade stenosis (peak-velocity ratio<2.0) in pulse wave doppler sonography, to minimize the effect of severe arterial wave reflections in distal blood pulse waves. Furthermore, PAD patients had to have a normal ankle-brachial index (ABI>0.9) after the intervention. In a previous population-based study, a low ABI was associated with low values of lower-limb PWV [24] and, possibly due to "falsely" low PWV values, attributable to the stenosis reducing blood flow and distending pressure downstream [25]. The control group volunteers were considered healthy if they had no history of cardiovascular disease and had not taken any cardiovascular drugs. Prior to MRI, PAD was excluded by means of pulse palpation and the ABI was between 0.9 and 1.3. The local ethics committee approved the protocol and all subjects gave written informed consent.

MR sequence parameters

All measurements were performed on a 3T MRI scanner (Magnetom Skyra; Siemens Heathineers, Erlangen, Germany) with an 18-channel receiver body coil array wound around the target limb. A 3D non-contrast magnetic resonance angiography (NATIVE, TOF) sequence was acquired to localize the superficial femoral artery. Four-dimensional flow phase contrast was acquired without contrast agent using the following scanning parameters: FOV=256×256 mm^2, matrix size (in-plane base resolution)=192×192 (1.3×1.3 mm^2), 12–18 slices, slice thickness (1.5 mm), TR=20–40 ms, TE=3 ms, bandwidth=490 Hz/px, and flip angle=7°. The velocity encoding (VENC) was set to 100 cm/s in the vessels of interest, according to the maximum flow velocity of the superficial femoral artery measured by previous ultrasound examinations.

The R-wave of the electrocardiogram was used to retrospectively trigger the 4D flow measurement with 14–22 timeframes acquired in the R–R interval dependent on the heart rate. The total time of the MRI examination including patient preparation took approximately 20 min. The total scan time of the 4D flow took approximately 7.8±2.1 min depending on the subject's heart rate. The approximate post processing time was 5 minutes.

Image processing

The data were analyzed using the CVI42 platform and MATLAB softwares (The MathWorks; Natick, MA, USA)

to generate hemodynamic parameters. First, the artery was semi-automatic segmented using maximal intensity projections on the phase images for every slice. The maximal velocity of every slice in the superficial femoral artery is calculated and within a 9×9 neighborhood, all pixels with a velocity higher than 50% of the local maximal velocity were taken for artery segmentation. The segmentation is represented as a vectorized line, which is then vectorially multiplied with the velocity field, which leads to the velocity over the distance along the artery.

The PWV is defined as the distance between two positions in the artery over their arrival time of one bolus. The PWV was estimated as the average along the entire segment of the superfical femoral artery assessed with the MRI of approximately 20 cm as shown in Figure 1. The arrival time was estimated by the foot-to-foot method. The foot-to-foot method is fitting the upslope of the wave profile by the tangential intersection to estimate the "foot" of the wave. The relation between arrival time and position in the artery results in the global (whole artery) and the local (step-wise division) PWV derived by linear fitting.

Ethics

This study was approved by the local institutional review board (identifier: 2019-740 N), and written, informed consent was obtained prior to scanning from all subjects. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation guideline. Data protection was in accordance with the EU Data Protection Directive.

Statistical analysis

Demographic and clinical characteristics of the study population are reported as means and standard deviations (SD) or as medians and (interquartile) ranges for continuous variables, according to their distribution. Categorical data are given as counts and percentages. The Mann-Whitney U-test was applied to determine significant differences between non-parametric continuous variables (PWV). p-values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 23 (IBM, Munich, Germany).

Results

Baseline characteristics of the study population

Seven PAD patients (four male, three female) were enrolled in this study (mean age 72±10). Baseline characteristics of the study participants are presented in Table I. At baseline, all patients had intermittent claudication in Fontaine stage IIb. The most frequent comorbid conditions and cardiovascular risk factors were: dyslipidemia (100%), hypertension (86%), and diabetes (57%); four patients had a history of nicotine consumption (57%), and one patient was active smoker. All patients received statins, and antiplatelet drugs, and one patient in the PAD group received oral anticoagulant therapy. According to lesion characteristics, the mean lesion length was 18.0±6.8 cm,

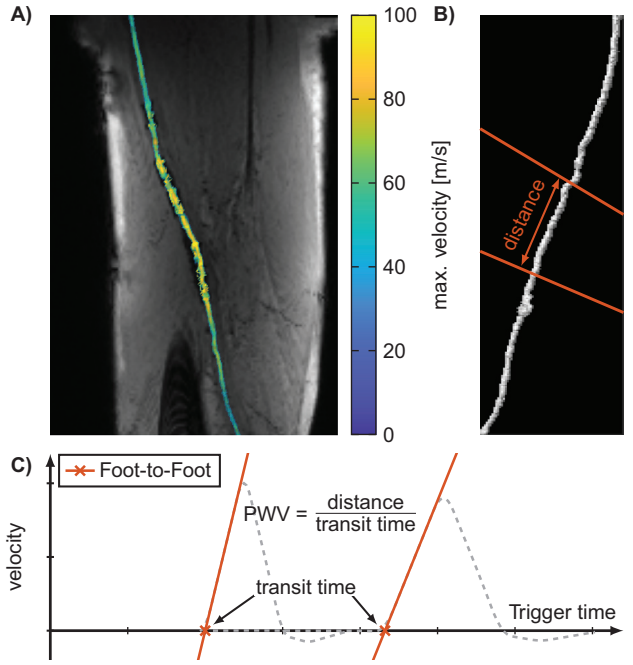

Figure 1. Illustration of regional pulse wave velocity (PWV) measurement principle. First, flow velocities overlayed on an anatomical maximal intensity projection of the 4D-flow data are assessed (A). Together with the distance measurement along the femoral artery (B) PWV is calculated as the distance between the two recording sites divided by the transit time between the feet of the two waveforms (C).

Table I. Baseline characteristics across the PAD group

Patient characteristics	
Age, years (mean±SD)	72±10
Male, n (%)	4 (57)
Intermittent claudication, n (%)	7 (100)
ABI postinterventional, prior to 4D-flow MRI	0.92±0.25
Chronic renal insufficiency, (GFR<60 mL/min), n (%)	2 (29)
Diabetes mellitus, n (%)	4 (57)
Hypertension, n (%)	6 (86)
Hyperlipidaemia, n (%)	7 (100)
Ex- or active nicotine consumption, n (%)	4 (57)
Lesion characteristics	
Lesion length, cm (mean±SD)	18.0±6.8
Reference lumen diameter	5.6±0.8
Severe calcification*, n (%)	4 (57)
Total occlusion, n (%)	2 (29)
VascuFlex® Multi-LOC stents implanted per lesion, mean±SD	5.0±0.7
Two or three crural vessel run-off, n (%)	7 (100)

SD: Standard deviation; ABI: ankle-brachial-index; GFR: glomerular filtration rate. *Fluoroscopic visualization of target lesion calcification.

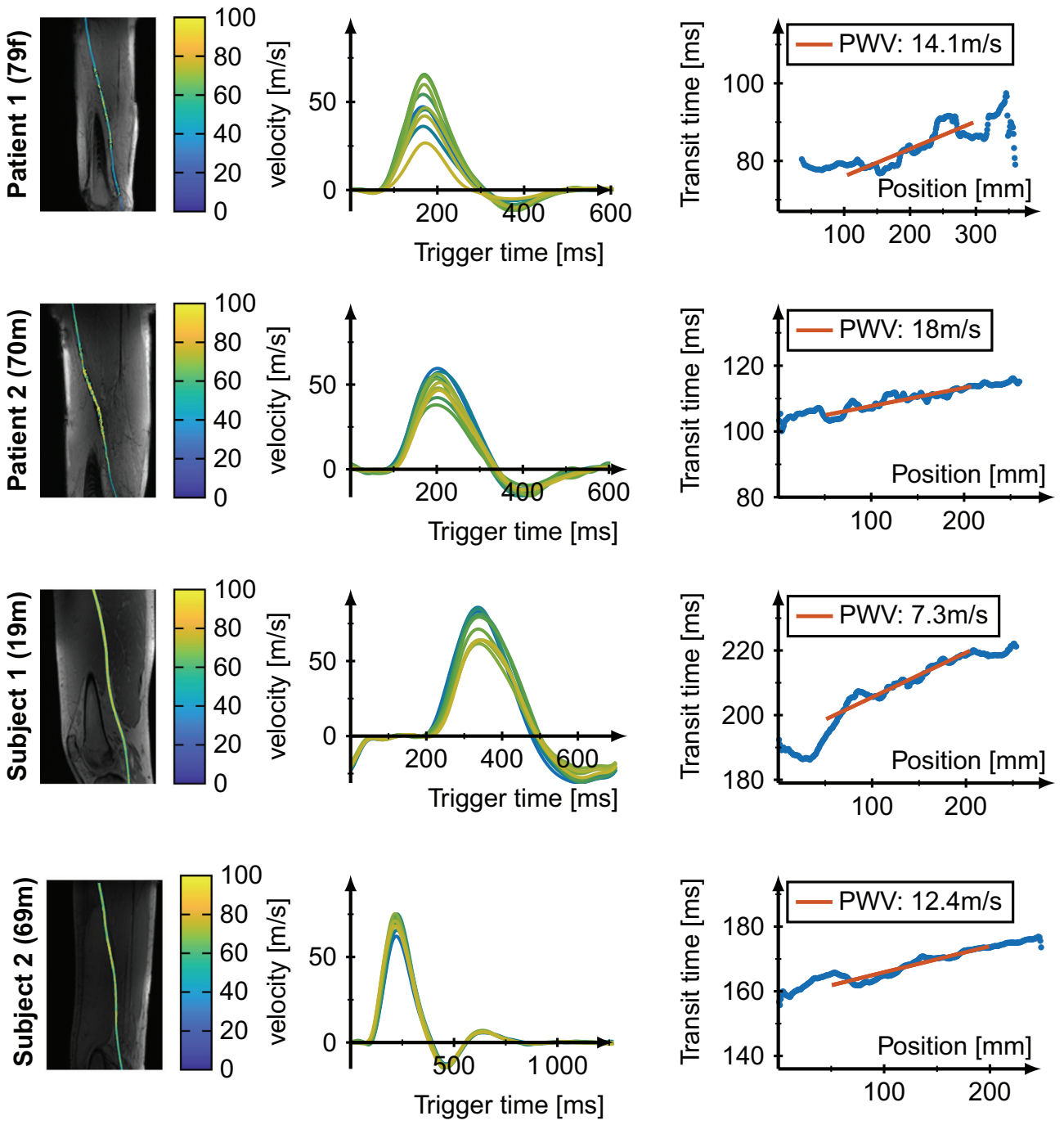

Figure 2. Flow velocity overlayed on anatomical maximum intensity projection of the 4D-flow data. These cases showed that the assessment of hemodynamic parameters in 4D-flow MRI is feasible not only in healthy subjects but also in PAD patients after multiple focal stenting of the superficial femoral artery. The flow velocity is depicted over the trigger time and encoded in color shading from blue to yellow for increasing distance to the proximal measurement. The transit times over the position in the femoral artery are plotted with the linear fit, resulting in the corresponding pulse wave velocities.

and two patients had chronic total occlusions. The mean number of "spot" stents implanted was 5.0±0.8 per lesion.

Comparison of the femoral PWV among groups

PWV was calculated using the time-to-foot method, examples are shown in Figure 2. PWV values across all groups were 15.6±5.2 m/s, 13.3±4.1 m/s, and 9.9±2.2 m/s in PAD patients, senior-aged volunteers, and young-adult volunteers respectively (Figure 3).

PWV values in PAD patients were similar to those in the senior-aged volunteer group (15.6±5.2 vs. 13.3±4.1, p=0.43). When compared to the young-adult volunteers, the senior-aged volunteers had a numerically higher mean local PWV (13.3±4.1 vs. 9.9±2.2, p=0.13). Despite the relatively small sample size, the differences between the young-adult volunteers and the PAD patients were statistically significant (p<0.05).

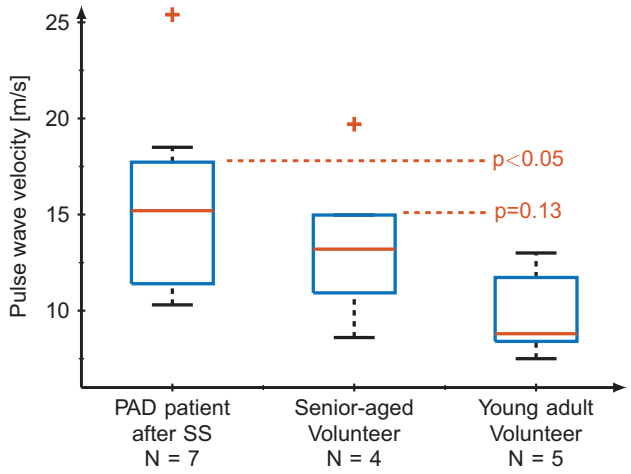

Figure 3. Pulse wave velocity values of the PAD patients as well as the senior-aged and young-adult control subjects are depicted in a box plot. Between PAD patients and the young-adult control is a significant difference of p<0.05.

Discussion

4D-flow MRI is an emerging tool for the evaluation of vascular hemodynamics. It measures the flow velocity in three directions for every voxel directly in vivo and, together with the distance measurement along the femoral artery, enables the calculation of the local PWV as an expression of the stiffness of an arterial segment.

Our study showed that 4D-flow MRI for estimation of segmental PWV in focally stented femoral arteries is feasible and that PAD patients with focally stented FP arteries but also senior-aged volunteers have higher PWV than young adult volunteers.

Feasibility

Generally, a small vessel diameter and high blood flow velocities are major challenges for quantification of flow velocity measurements and estimation of PWVs by means of functional MRI. This can be overcome by MRI sequences offering high spatial and temporal resolution, facilitating local PWV measurements [26]. Further, metallic vessel scaffolding makes it difficult to adequately assess the vascular lumen for blood flow analysis [21]. This additionally complicates the biomechanical assessment of the FP artery after stent-based interventions, especially after full-metal jacket stenting. The SS technique was developed with the aim of influencing the FP biomechanical properties as little as possible. To record the latter in vivo is challenging. Today, a substantial part of the findings on how stents change the biomechanics inside or outside the stent segments is based on perfused human cadaver models [14]. The SS strategy offers MRI "windows" in the inter-stent segments. In the present study, the feasibility of estimation of hemodynamic parameters and local PWV as a surrogate of vascular stiffness in FP arteries after SS was shown for the first time. Employing 4D flow MRI systems offer several advantages over other techniques for local PWV assessment: It is non-invasive, free from ionizing radiation and provides a direct, 3-dimensional measurement of the path length of pulse wave trajectory, even from anatomically deep and tortuous arteries.

PWV values

Generally, the values of local PWVs for peripheral arteries (e.g. the femoral artery) are higher compared to the central arteries (e.g. the aorta and carotid artery). Causes for this encompass the muscular nature of peripheral artery walls together with their smaller cross-sectional area and the influence of wave reflections [23]. While PWV estimates from central arteries have emerged as a powerful independent predictor of cardiovascular outcomes [27, 28], local PWV estimates from peripheral arteries in PAD patients might be an early step towards a deeper understanding of the diseased vessels' characteristics and the impact of stent deployment. Further studies to systematically compare local PWV measures in patients after FP stenting and in patients after non-stent based treatment strategies are planned. In principle, MRI provides the possibility to visualise and measure even more biomarkers such as peak systolic velocity and wall shear stress [29].

Until today, no methodological standardization has been established globally for determining the gold-standard of local vessel stiffness measurements of individual arteries. Extensive comparative studies on the accuracy of the available methods are lacking. Generally, invasive techniques for local PWV measurement – capturing hemodynamic signals from the target artery – are considered to provide the gold-standard estimate. Similar to non-invasive methods of arterial pulse waveform assessment for PWV measurement using applanation tonometry, cuff-based or echo-tracking techniques and current 4D-flow protocols, there is a lack of standardization of local PWV measurement and reference values for lower-extremity arteries [26].

In our study on superficial femoral arteries, the mean PWV in the young-adult group (9.9 m/s) aged between 19 and 28 years was in close agreement with those reported by Bustin et al. (mean 9.8 m/s) for the<29 years group [30]. The mean segmental PWV values of the PAD patients (15.6 m/s) were approximately 50% higher. According to the Bramwell–Hill derived equation (Compliance=k/PWV^2; [31]) an increase of PWV in that range means more than doubling arterial stiffness. Previously reported data regarding the aging of the lower-extremity arteries are discrepant. Overall the stiffness of lower-extremity arteries seems to be affected to a lesser extent by age compared to central arteries [32]. In an epidemiological study in more than 5,000 healthy individuals, femoral stiffness was shown to remain constant over many years, but to increase significantly between the sixth and eighth decade, which matches our results [33]. The mean segmental PWV values of the senior-aged control group (13.3 m/s) were not far from that of the PAD patients (15.6 m/s).

Limitations

Aside from the small number of subjects studied, our study has several limitations concerning this issue. First, the study groups were small in number, not extensively pre-examined cardiovascular or heterogeneous. Our control subjects were neither screened for cardiovascular risk factors nor was vascular calcification assessed. The latter is known to be associated with age and can begin at a young age and has to be distinguished from atherosclerotic occlusive disease [34]. However, given the lack of consensus on the definition of calcification and classification of its burden, especially in the healthy, we dispensed with further examinations in this feasibility study. All PAD patients were treated for major cardiovascular risk factors, including statins, which are known to reduce lower-limb PWV [35, 36]. First, reliable local PWV measurement techniques are needed to achieve accurate performance under in-vivo conditions. Second, larger studies are required to make deductions concerning local PWV associated with PAD. Finally, future research is warranted to standardize and validate the method and evaluate the clinical utility of local PWV.

Conclusions

Contrast-free 4D-flow MRI provides a high spatiotemporal resolution that allows the assessment of hemodynamics in focally stented as well as in native FP arteries. Calculating segmental PWVs in the FP artery segment is feasible in PAD patients with multiple spot stents. The PWV values in PAD patients were similar to those in senior-aged volunteers, both of which were higher than in young-adult volunteers.

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Conflict of interest
KA has received lecturer honoraria and research grants from B. Braun. He is co-inventor of a patent application for the "Multi-LOC" stents used in this study.

Authorship
Ingo Hermann and Tetyana Shchetynska-Marinova contributed equally to this work, the ordering of the two authors is alphabetical.

ORCID
Martin Sigl
https://orcid.org/0000-0001-6162-6304

Correspondence address
Dr. Martin Sigl, MD
Section Chief Angiology, First Department of Medicine
University Vascular Center Mannheim
Theodor-Kutzer-Ufer 1-3
68167 Mannheim
Germany

martin.sigl@umm.de

Case report

Implantation of vascular mimetic implants in challenging chronic total occlusions – Supera™ Extreme

Erwin Blessing, Muliadi Antaredja, Lisa Tilemann, and Ralph Oberacker

Department of Internal Medicine, Vascular Center, SRH Klinikum Karlsbad-Langensteinbach, Karlsbad, Germany

Summary: Standard nitinol stents (SNS), with or without drug eluting technology, are an essential tool within the interventional armamentarium in the treatment of patients with peripheral arterial disease. However, they are plagued by a number of limitations: a.) stent fractures, although observed predominately in first-generation stents, do still occur in state-of-the art stent platforms, b.) lack of radial strength, resulting in inadequate stent expansion, c.) kinking up to a complete collapse of the stent, therefore compromising its use in areas of high mechanical stress such as bending zones. In contrast, the interwoven design of the Supera™ stent, also referred to as "vascular mimetic implant", overcomes all of the above limitations of SNS. Several registries and studies not only confirmed its mechanical superiority (lack of stent fractures etc.) but also demonstrated remarkable clinical performance (patency and freedom from target lesion revascularization), despite its use in challenging lesions (calcification etc.) and territories (popliteal arteries etc.). Increasing confidence in the mechanical properties of the Supera™ stent platform prompted interventionalists to further "push the limits" of this unique implant. The present article summarizes the clinical data and shows examples of "extreme" applications of this dedicated stent platform.

Keywords: Vascular mimetic implants, peripheral arterial disease, chronic total occlusions

Introduction

In the era of drug eluting balloon technology, primary stent implantation got more and more replaced by proper lesion preparation followed by anti-restenotic therapy and, if needed, "bail-out" stent implantation. The later approach reduces the number of stents implanted within the lesion and/or the length of lesion that requires scaffolding (spotted stenting). Reasons for "bail-out" stenting are either a.) residual stenosis >30% or b.) presence of flow limiting dissection despite adequate efforts of lesion preparation. SNS are the standard of care implant to overcome the above-mentioned challenges. Long term performance of first generation SNS was compromised by rather frequently observed stent fractures that were clearly associated with loss of patency [1]. Although newest generation nitinol stents show improved fracture resistance, they are still reported to be in the range of several percent [2]. Limited radial strength of SNS frequently results in inadequate stent expansion, if deployed in heavily calcified or fibrotic lesions. Naturally, residual stenosis due to inadequate expansion of the scaffold results in suboptimal improvement of clinical symptoms and/or triggers target lesion re-revascularizations. Finally, if implanted in areas with high mechanical stress such as bending zones, crushing of SNS can result in complete cease of blood flow. In contrast, the Supera™ stent has a braided nickel-titanium alloy design to withstand the stressors along the course of the femoropopliteal segment [3]. It is an almost completely fracture resistant implant that delivers a several-fold higher radial strength and a higher crush resistance compared to SNS. We report a series of 3 patients, demonstrating the more advanced use of this dedicated stent platform.

Case reports

Case example 1

A 63-year old male patient with arterial hypertension and hyperlipidemia presented with claudicatio of the left calf after 200 meters (Rutherford 3) and an ankle-brachial index of 0.5 on the left side. His previous medical history was significant for coronary artery disease, chronic kidney disease and bilateral renal artery stenting. Regarding the lower extremity, an endovascular procedure was performed more than 20 years ago, when a standard nitinol stent was placed in the left common femoral artery, extending into the deep femoral artery (Figure 1A). Revascularization of the occluded proximal superficial artery was therefore complicated by the previously implanted stent. Treatment of the moderate instent restenosis was performed with a scoring balloon (Angiosculpt™ 6 × 40 mm, Biotronik) and a drug eluting balloon (InPact

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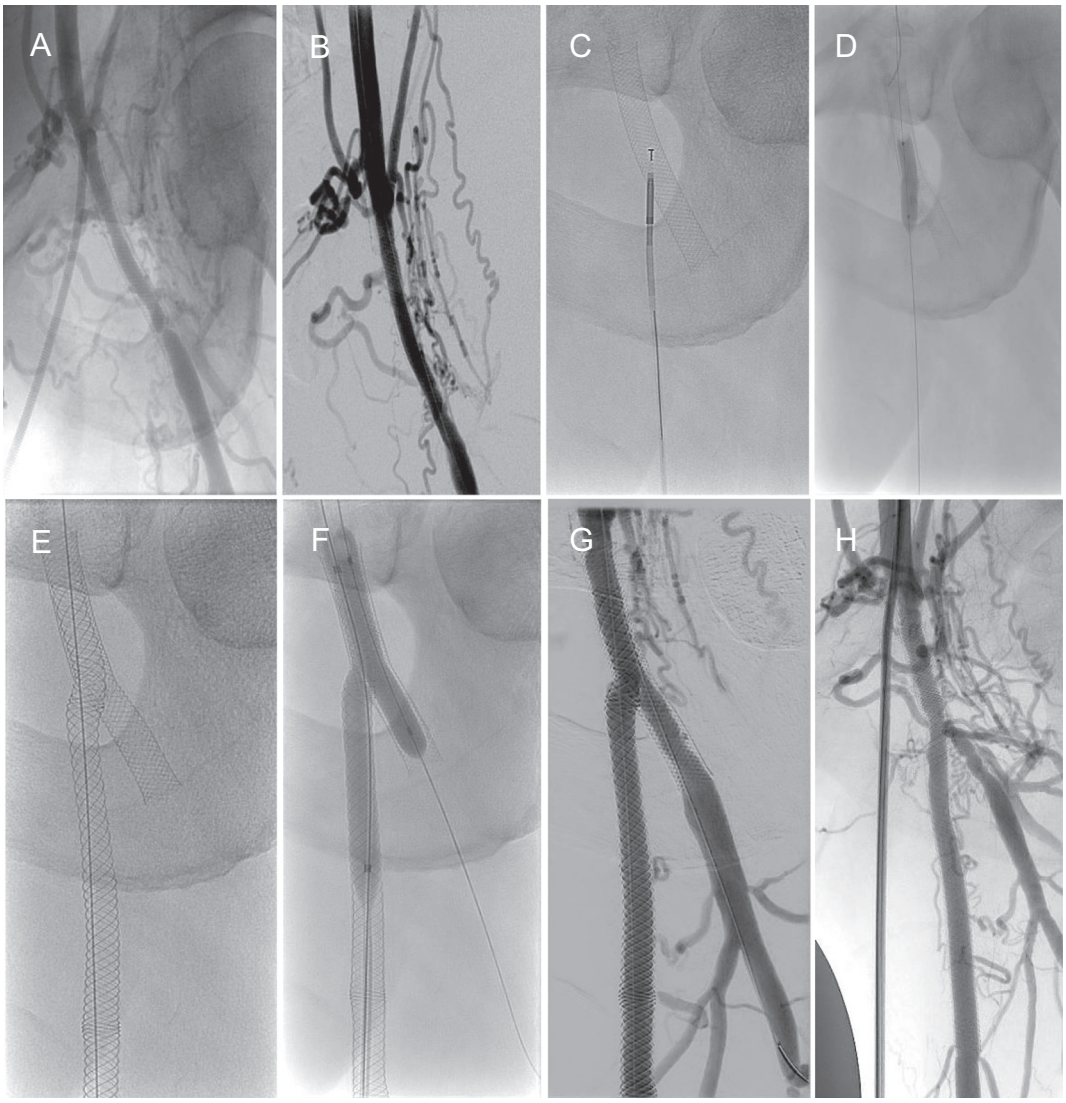

Figure 1. A previously implanted standard nitinol stent extended from the common femoral artery into the deep femoral artery (A). The distal superficial femoral artery was filled via collaterals (B). An Outback re-entry device was placed in a reversed fashion via the distal femoral artery (C). After successful retrograde wire passage, standard balloon inflations were performed (D) to prepare the lesion for Supera stent implantation in the Culotte technique (E), followed by kissing balloon inflations (F). Acute angiographic result was excellent (G). 24-months follow up showed mild in-stent restenosis of the standard nitinol stent, extending into the deep femoral artery (H).

Admiral™, 6 × 60 mm, Medtronic). We then opted for an additional retrograde access via the patent distal superficial femoral artery with a 6 F sheath and a dedicated re-entry device (Outback™, Cardinal Health) to precisely enter the common femoral artery at the area of the origin (Figure 1B). After successful wire passage, dilatations with increasing balloon sizes were performed. Residual stenosis despite prolonged balloon inflations prompted us to place a Supera™ stent (6.5 × 80 mm) via the retrograde access (Figure 1C), using the Culotte technique [11]. After final kissing balloon inflations (Figure 1D), an acceptable angiographic outcome could be achieved (Figure 1E). Patient was discharged on the next day without impaired walking capacity. Ankle-brachial index immediately improved to 0.9. Patient returned for an intervention of the contralateral side 24 months later. Angiography of the left groin confirmed patency of the stented bifurcation with only moderate in-stent restenosis (Figure 1F).

Case example 2

An 86-year old fragile lady presented with rest pain (Rutherford 4) of the left leg. Her co-morbidities included coronary artery disease with previous myocardial infarction. Duplex sonography showed a calcified occlusion of the left common femoral artery and of the left superficial femoral artery. Ankle-brachial index on the left side was 0.5. After she refused open vascular surgery for the left groin, we offered an endovascular approach. Angiography confirmed the massively calcified occlusion of the common femoral artery and a filling of 2 main branches of the deep femoral artery via collaterals (Figure 2A). Antegrade wire passage through the occluded common femoral artery could not be achieved via the crossover approach, but through a retrograde access via the distal left superficial femoral artery. To allow retrograde wire passage, we performed inflations of a low-profile balloon

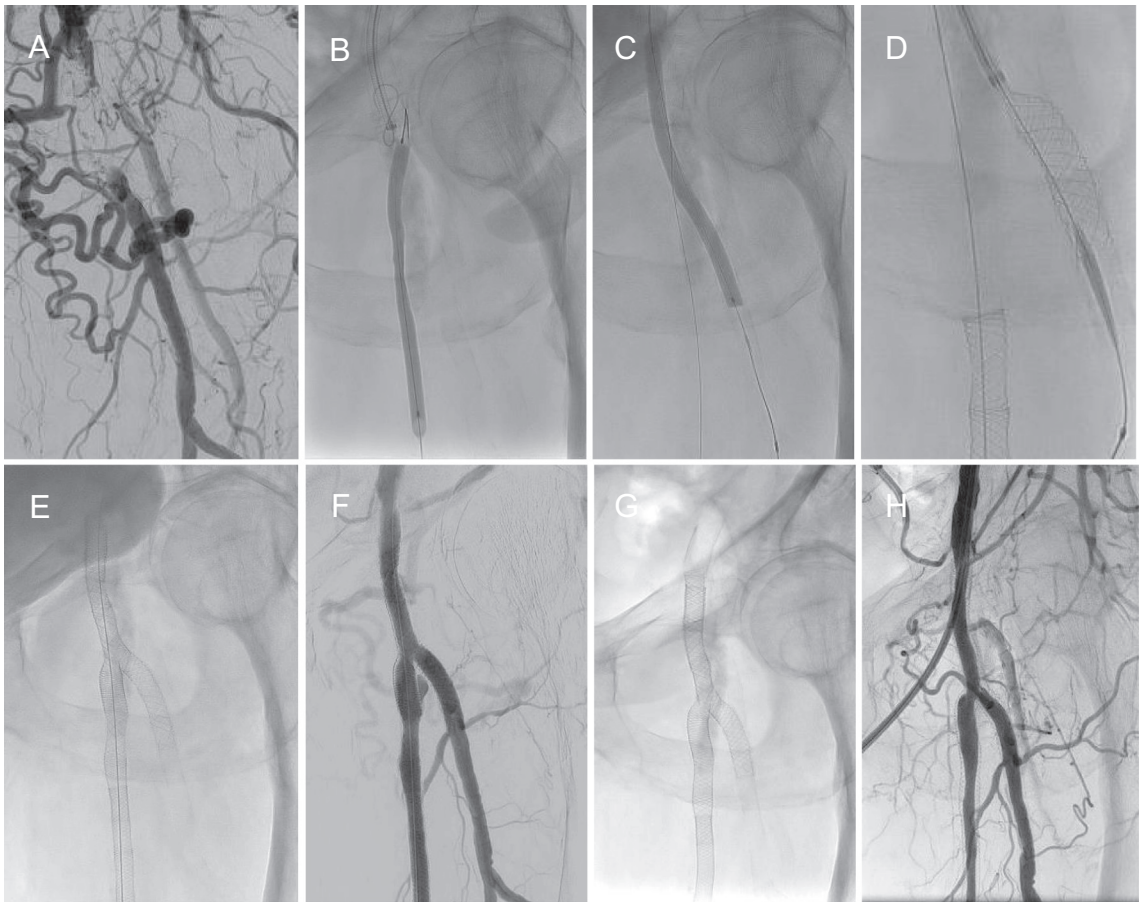

Figure 2. Angiography of an elderly lady with rest pain showed a calcified occlusion of the common femoral artery (A). Retrograde wire passage was successful via the distal superficial femoral artery (B) and via the deep femoral artery (C). Following wire externalization, 2 Supera stents were placed via the crossover sheath, one in the superficial femoral artery and one into the deep femoral artery, extending into the common femoral artery (D). Finally, another Supera stent was placed into the proximal femoral artery, extending into the common femoral artery using the Culotte technique (E) with excellent angiographic result (F). Rest pain immediately resolved, and angiography after 18 months confirmed patency of the left bifurcation with only moderate in-stent restenosis (G and H).

(Armada 4 × 80 mm, Abbott Medical), (Figure 2B), introduced sheathlessly via the distal superficial femoral artery. To avoid compromization of the deep femoral artery, we opted for an additional retrograde access through one of the main branches with a 21 G needle, a V18 wire (Boston Scientific) and 0.018″ support catheter (Cook CXI™) (Figure 2C). Since both retrograde wires were within the subintimal space at the level of the common femoral artery, we decided against a debulking strategy (directional atherectomy etc.). After predilation we first placed a 5.5 × 200 mm Supera™ stent in the mid to distal part of the superficial femoral artery and a 6.5 × 60 mm Supera™ stent from one of main branches of the deep femoral artery into the common femoral artery (Figure 2D). Finally, after re-wiring and predilatation, we implanted a 6.5 × 80 mm Supera™ stent in the proximal superficial femoral artery, extending into the common femoral artery using the Culotte technique (Figures 2E and 2F). All stents were placed via the crossover sheath from the contralateral side. Haemostasis of both the distal superficial and the deep femoral artery was achieved with low pressure balloon inflations and external manual compression. The rest pain immediately improved and the lady was free of symptoms on the left leg at various follow up visits. 18 months after the procedure, the patient underwent intervention of the right leg via crossover approach. Puncture of the Supera™ stents and placement of the crossover sheath was uneventful. Angiography confirmed patency of the left bifurcation with only moderate in-stent restenosis (Figures 2G and 2H). At the most recent clinical follow up (2½ years after the intervention) the patient still did fine with a left ankle-brachial index of 0.93.

Case example 3

An 81-year old lady presented with non-healing ulceration of the right lateral malleolus. Previous vascular history was significant for endarterectomy and profunda plastic of the right groin one year prior to presentation. Co-morbidities included coronary artery disease. Pre-interventional workup showed a long occlusion of the right superficial femoral artery (duplex and MRI) and an ankle-brachial index of 0.5. Crossover access via the left groin confirmed patency of the prosthesis and a lack of any antegrade recanalization options for the occluded superficial femoral artery (Figure 3A). We therefore opted for a retrograde access via the distal right superficial femoral artery. Re-entry of the retrograde wire was not successful due to

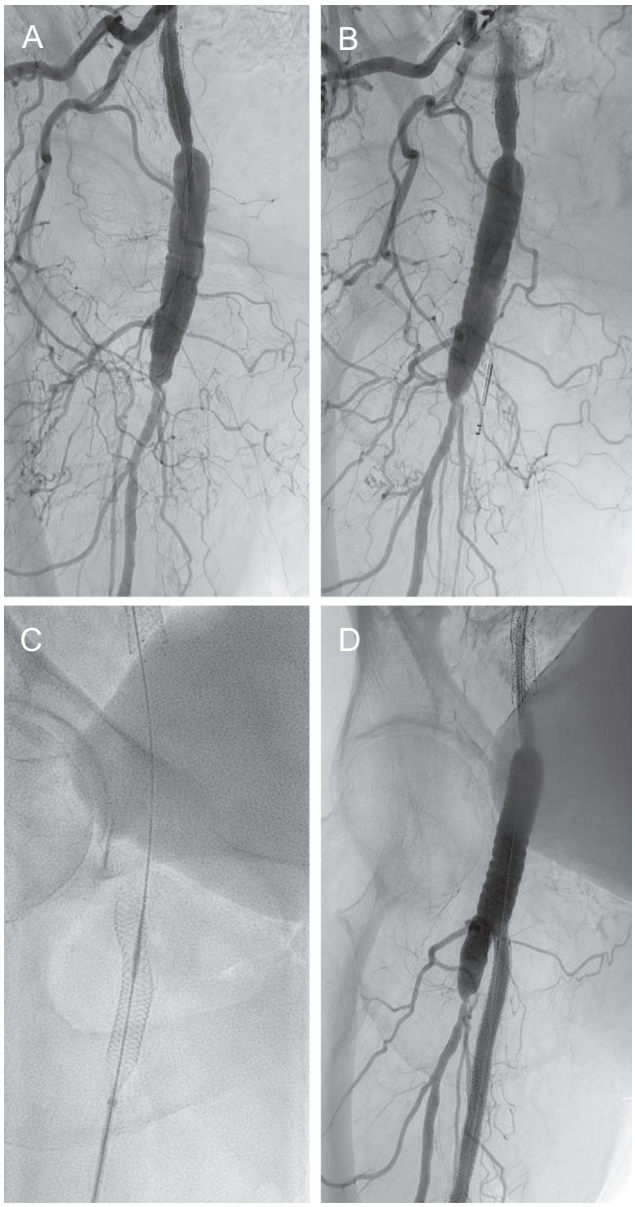

Figure 3. In a patient with critical limb ischemia many years after groin surgery, crossover access via the left groin confirmed patency of the prosthesis and a lack of any antegrade recanalization options for the occluded superficial femoral artery (A). A low-profile re-entry device was advanced reversely via the distal superficial femoral artery, enabling precise puncturing and wire entry into the prosthetic graft (B). After wire externalization and predilatations with high-pressure balloons, a Supera stent was deployed reversely (C) into the proximal superficial femoral artery with excellent final angiographic result (D).

scar formation after previous vascular surgery. A GoBack™ catheter (Upstream Peripheral Technologies Ltd.), a dedicated low-profile re-entry device enabled precise puncturing and wire entry into the prosthetic graft (Figure 3B). After wire externalization and predilatations with high-pressure balloons, a Supera™ stent (6.5 × 150 mm) was advanced sheathlessly via the retrograde route and deployed reversely (Figure 3C). The so-called PRESTO-technique allowed accurate coverage of the take-off of the superficial femoral artery. Exceptional radial strength of the Supera™ stent prevented recoil even in the area of severe fibrosis, as generally observed after open vascular surgery (Figure 3D). The delivery system of the stent was removed and replaced by a long 4 F sheath, matching the outer diameter of the stent shaft and therefore achieving temporary haemostasis. At the end of the intervention, a low-pressure balloon inflation at site of retrograde vessel access was performed in the distal superficial femoral artery for 5 min to achieve haemostasis. The ulceration at the right malleolus completely resolved within weeks.

Discussion

The dedicated interwoven stent platform Supera™ helped to overcome well-described limitations of standard nitinol stents in three challenging situations. In the first case, the stent was deployed in a reversed fashion to create a bifurcation with a previously implanted stent in the common femoral artery. In the second case, 2 vascular mimetic implants were combined in a Culotte technique in a heavily calcified bifurcation lesion with favorable long term angiographic follow up. Finally, a reversed implanted Supera™ demonstrated excellent compression resistance even in an area of severe fibrosis in a patient in whom the proximal part of the superficial femoral artery was removed during previous surgery.

Acute technical success as well as long term clinical performance has been evaluated in several studies and registries. Patency rates of a large single center registry were reported to be as high as 83.3% and 72.8%, 12- and 24 months after Supera™ stent implantation [4]. Stent fractures were not observed, despite the complexity of lesions in this non-selected cohort. Similar patency rates were reported by the same group if the stent was implanted into the highly challenging popliteal artery [5]. The SUPERB trial, a large multicenter single-arm prospective registry confirmed the performance of the Supera™ stent with a high patency, absence of stent fractures, and improvement of functional parameters and quality-of-life measures [6] even up to 3 years follow up [7]. Increasing confidence in the interwoven stent platform encouraged interventionalists to evaluate the device in longer and even more complex lesions. In the "Supersub" study, Palena et al. implanted the device after intentional subintimal recanalization of chronic total occlusions in 34 patients with critical limb ischemia [8]. Patency was reported to be as high as 94.1% and freedom from target lesion revascularization 97.1% after 12 months in lesion with an average length of 27.9 cm.

One of the main limitations of the Supera™ stent is that it requires a careful lesion preparation, allowing a nominal deployment pattern of the interwoven stent platform. This can be achieved either by plaque removal (debulking) such as atherectomy or by the use of high-pressure balloons, matching the size of the outer diameter of the Supera™. Suboptimal deployment, in particular elongation of the stent is associated with decreased clinical performance of the device, as shown in a subgroup analysis of the SUPERB

trial[7]. In extremely calcified lesions, the so-called "pave-and-crack" technique can also be considered to avoid vessel rupture through standard high-pressure balloon inflations. Severely calcified lesions are first "paved" by an endoprothesis that prevents unprotected perforations through high pressure balloon inflations. Since standard endoprothesis do not necessarily prevent recoil of calcified lesions, a Supera™ stent is finally deployed within the Viabahn prothesis [9].

Another limitation is, that the exact position of the proximal ending of the stent is difficult to predict, since the actual length of the deployed stent depends on the above-mentioned deployment pattern. Even in experienced hands, a minimal variation of the deployment cannot be fully avoided. Therefore, placing a Supera™ stent exactly e.g. at the ostium of the superficial femoral artery remains challenging. To overcome this limitation, the so-called PRESTO technique (precise retrograde Supera™ stenting of the ostium) was first described by Palena et al. [10]. After retrograde access via either the distal superficial femoral artery or a proximal below-the-knee artery, the "first throw" of the stent can be precisely placed where needed to fully cover the origin of the superficial femoral artery while avoiding overstenting of the deep femoral artery.

Fracture-resistance and the fact, that the single wire interwoven design allows puncturing and sheath placement through the struts potentially qualifies the Supera™ stent to be used also in the common femoral artery. The ongoing Supera™ CFA-VMI study showed excellent technical success and patency rates after 24 months. Obviously, long-term follow up data are needed to support the more liberal stent use in this challenging territory. Although bifurcation stenting is often not required, even if the deep femoral artery is involved, the unique properties of the Supera stent allow the combination with a SNS or 2 Supera™ stents using different bifurcation techniques. The so-called "Culotte" technique can be applied with Supera™ stents, if scaffolding of both the deep and the superficial artery is mandatory. In a first report in 1998 Chevalier et al. described the method in coronary arteries. Stents are placed both in the main branch and the side branch, with the 2 stents overlapping in the main branch before the bifurcation [11]. The Culotte technique can also be adapted in bifurcation lesion in the peripheral anatomy with Supera™ stents.

Conclusions

Despite efforts to avoid primary stent implantation, treatment of complex lesions (long lesions, severely calcified or fibrotic lesions etc.), still often requires "bail-out" stenting. In the presence of calcium and/or in bending zones, the interwoven nitinol stent Supera™, offers an excellent treatment modality that overcomes well described limitations of standard nitinol stents. Supera™ stent implantation allowed both excellent acute results as well as favorable long-term clinical outcomes in our extremely challenging cases.

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ORCID
Erwin Blessing
https://orcid.org/0000-0003-0205-9084

Correspondence address
Prof. Dr. med. Erwin Blessing
SRH Klinikum Karlsbad-Langensteinbach
Guttmannstr. 1
76307 Karlsbad
Germany

erwin_blessing@yahoo.de

Erratum

Correction to Mühlberger et al. (2020)

In the article entitled "External valvuloplasty of the saphenofemoral junction in insufficient great saphenous veins – six weeks results of a prospective multicentre trial" by D. Mühlberger, E. Brenner, H. Brockhoff, N. Frings, B. Geier, A. Mumme, S. Reich-Schupke, A. L. Rohrer, H.-P. Steffen, D. Stenger, M. Stücker and T. Hummel (*Vasa, 49,* 411–417, https://doi.org/10.1024/0301-1526/a000874) the registry number of the ethical approval was given incorrectly on the second page of the print and PDF version. The correct registry number is 5034-14 instead of 5024-14.

The authors regret any inconvenience or confusion this error may have caused.

Reference

Mühlberger D, Brenner E, Brockhoff H, Frings N, Geier B, Mumme A, et al. External valvuloplasty of the saphenofemoral junction in insufficient great saphenous veins – six weeks results of a prospective multicentre trial. VASA. 2020;49(5):411–7. https://doi.org/10.1024/0301-1526/a000874

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Letter to the editor

A questionnaire survey study on nail disease prevalence in patients under podologic foot care

Annett Biedermann[1], Eickmann Beate[2], Eirich Monika[3], Schwab Gabriele[3], Anja Bomba[4], Yannic Binan Abdollah-Zadeh[5], Mertens R. Peter[6], and Knut Kröger[5] for the Deutscher Verband für Podologie (ZFD) e.V.

[1] Podologic Office, Straßfurt, Germany
[2] Podologic Office, Hamm, Germany
[3] Podologic Office, Friedberg, Germany
[4] Medical Information Management, Fliedner Fachhochschule, Düsseldorf, Germany
[5] Clinic for Vascular Medicine, HELIOS Klinik, Krefeld, Germany
[6] University Clinic for Nephrology and Hypertension, Diabetology and Endocrinology, Otto-von-Guericke Universität, Magdeburg, Germany

Nail disorders (ND) are frequent among the geriatric population but our knowledge about underlying diseases causing specific ND is low [1, 2, 3, 4, 5]. We therefore analyzed ND in patients presenting for podologic treatment in an outpatient setting in Germany. The setting of podologic care in Germany is unique, given that a specialist nurse, the so-called podologist, who has passed a three-year training curriculum in foot care, especially with patients suffering from diabetes mellitus (DM), are providing this care in private outpatient settings. In contrast to podiatrists, podologists are not allowed to use a scalpel or other instruments for perform active debridements that goes along with bleeding.

The questionnaire asked for 16 specific NDs and some additional patient characteristics, including gender, age, height and weight. To ease uniform definition of underlying ND and to standardize the repertoire of possible answers a priori list of specific NDs was included with definitions for each disorder aside Electronic supplementary material [ESM] 1. Because of missing data final data set included 1619 cases.

Of all reported "cases" onychomykoses were diagnosed in 30.7%, ungius convolutes in 41.8%, onychauxis in 29.4%, onycholyses in 13.4% and ungius incarnatus in 22.5%. DM as a comorbidity was present in 60.3%, peripheral polyneuropathy (PNP) in 48.9%, peripheral arterial disease (PAD) in 29.9%, congestive heart disease with signs of heart failure (HI) in 29.7%, obesity in 29.7% and lymphedema (LE) in 21.9% of reports. With advanced age onychomycosis and onychausis was more likely, but not the others (ESM 2). Male gender was more likely to be associated with onychomycosis, whereas in females unguis convolutus, onycholysis and unguis incarnatus were reported more frequently. Diagnosis of DM was more likely with onychomycosis and unguis convolutus, however not unguis incarnatus. High body mass index >30 (obesity) was associated with diagnosis of unguis convolutus and onychauxis.

A final regression analyses shows that specific ND was mostly associated with gender: male patients presented more frequently with onychomycosis, but less frequently with onycholysis, unguis convolutus and incarnatus (ESM 3). An age >75 years was associated with a higher prevalence of onychomycosis whereas obesity was associated with unguis convolutus. The comorbidities DM, PNP, PAD and LE were not associated with the considered ND. In contrast, heart insufficiency is associated with onychomycosis, onycholysis, onychauxis and unguis convolutus.

The main findings of the questionnaire survey reveal that gender has a higher impact on type of ND than advanced age. With advanced age a predisposition for onychomycosis exist, whereas in females onycholysis and unguis convolutus and incarnatus are more prevalent. Unexpectedly, the impact of comorbidities such as DM, PAD, PNP and LE for specific ND is low, only with heart failure and congestive heart disease the prevalence of onychomycosis, onychausis, onycholyis and unguis convolutus increases.

A limitation of the survey that it specifically addresses the professional environment and patient cohort cared for by podologists in Germany and all data regarding comorbidities are based on personal information and not on medical reporting. Confirmation of comorbidities was not performed, also the severity was not assessed. Furthermore, diagnosis of ND relied on the expertise of the podologists only. Although these are well trained in

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diagnosing ND, the accuracy of the diagnoses only relied on their judgement and knowledge.

Prevention of ND requires knowledge of the kind and timing of diseases. Our survey questionnaire study reveals that gender has a strong impact on the type of ND, to a lesser degree advanced age and obesity changes the type of ND. Furthermore, the comorbidity of congestive heart disease and heart failure may require additional attention regarding the occurrence of ND, which may likely results from chronic limb ischemia and edema formation in the legs.

Electronic supplementary material

The electronic supplementary material (ESM) is available with the online version of the article at https://doi.org/10.1024/0301-1526/a000967

ESM 1. Summary on comorbidities which were recorded from the medical forms of the patients and ND diagnosed by the podologists (Table)

ESM 2. Frequency of nail disorders in dependence of age, gender, BMI and diagnosis of DM (Table)

ESM 3. Frequency and associations of patient characteristics and comorbidities with nail disorders (Table)

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Correspondence address
Prof. Dr. med. Knut Kröger
Klinik für Gefäßmedizin
HELIOS Klinikum Krefeld GmbH
Lutherplatz 40
47805 Krefeld
Germany

knut.kroeger@helios-kliniken.de

Journal club

No pain, no gain in PAD

Kristina Sonnenschein

Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany

More than 200 million people are affected by peripheral artery disease (PAD) worldwide [1]. The most common symptom affecting PAD patients is intermittent claudication. Besides medication and revascularization therapies, supervised walking exercise is recommended in the current national and international guidelines improving walking distance and quality of life of PAD patients [2, 3, 4]. Unfortunately, for various reasons, only few patients put this recommendation into practice and perform regular walking training. Because of poor adherence to high-intensity walking training, McDermott and colleagues tested in their LITE (low intensity exercise intervention in PAD) trial [5] the effect of light walking exercise at comfortable speed on the walking ability in PAD patients. The authors performed a multicenter randomized clinical trial in the USA including 305 patients with stable PAD. Study participants were randomized to low-intensity walking exercise group (n=116), high-intensity walking exercise group (n=124) or control group without exercise (n=65). Patients were followed up for 12 months. Patients in the both walking exercise groups were instructed to perform either high-intensity or low-intensity exercise training by monitoring their exercise intensity by an accelerometer. Participants of the high-intense group were instructed to go to their pain limit; participants of the low-intense group could run at a comfortable pace without ischemic leg symptoms. Both groups were asked to perform training exercise for five times per week for up to 50 minutes per session. Control patients only received intensive educational program to health topics.

The primary endpoint of the study was the change in the 6-minute walk distance after 12 months. The secondary endpoint was a composite endpoint containing changes in walk distance, walking time, speed and physical activity scores as well as adherence to the exercise training and histological changes in the patients' calf muscle biopsies. After 12 months, the high-intensity exercise group was significantly more effective in improving 6-minute walk distance compared to the low-intensity group (+34.5 m vs. −6.4 m, $p<0.001$). Although the low-intensity group exercised more often (3.5 vs. 2.8 days per week, $p<0.001$) and for more minutes per week (145 min vs. 77 min per week, $p<0.001$) there was no difference in 6-minute walk distance between the low-intensity and control group (−6.4 m vs. −15.1 m, $p=0.44$). With regard to the secondary endpoint, the high-intensity exercise group was more effective in comparison to the low-intensity and control group with exception of the Walking Impairment Questionnaire distance score (17.6 vs. 8.0, $p<0.009$), whereby this included a subjective assessment of difficulties in walking distances of PAD patients. In 47 patients who underwent calf muscle biopsies at baseline and after 12 months, there were no significant changes between high- and low-intensity exercise groups in the content of nitrotyrosine, citrate synthase and cytochrome C oxidase activity. The LITE study underlines the importance of intensive walking exercise and confirms the fact that not only supervised, but also home-based walking programs can be successful in PAD patients. The key to the success is the intensity and willingness to carry out the training regularly.

Even if this study by McDermott and colleagues gives these positive results for high-intensive exercise there are some limitations of the study. About 18% of PAD patients were lost to the 12-month follow-up and due to the COVID-19 pandemic further data on treadmill stress tests could not be collected in 2020. Moreover, there was a discrepancy between objective and subjective walking performance in the low-intensity walking group maybe due to the fact that this interventional study was not blinded. Additionally, even previous inactive PAD patients were motivated to walk regularly as part of the study and thereby their perceptions about their walking ability was subjectively influenced even in the low-intensity group. Despite the small number of patients, the LITE trial and the need of larger studies this is a further step towards confirming the home-based training concept and underlining the importance of the correct walking exercise intensity in the PAD patients. Therefore "No pain, no gain" can still be applied to our PAD patients.

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Correspondence address
Kristina Sonnenschein, MD
Hannover Medical School
Department of Cardiology and Angiology
Carl-Neuberg-Strasse 1
30625 Hannover
Germany

sonnenschein.kristina@mh-hannover.de

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