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Editorial

Finally, the big picture of morbidity and mortality in peripheral arterial disease?

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In the last decades, due to aging communities and worse risk factor profiles, incidences of peripheral artery disease (PAD) increased both in western and developing countries and are predicted to drastically increase globally in the next years [1,2]. Yet, PAD remains still highly undetected [3]. Moreover, definitions and diagnostic assessment of PAD widely differ in the current literature. Clinicians will agree that comparability between intermittent claudication (IC) and a low ankle-brachial index (ABI < 0.9), which might be asymptomatic, is not met. In addition, the diagnosis of critical limb ischemia (CLI) in diabetic patients with feet ulcers without vascular assessment is weak. In this minefield of problems, most of our evidence is derived from observational trials. Only a few randomized controlled trials like COMPASS-MI [4] and FOURIER [5] with distinct PAD subgroups contributed stronger evidence to our secondary prevention and therapy goals in PAD. Nevertheless, guidelines challenged us to improve treatment of PAD patients with stricter risk factor optimisation goals during the last decade [6,7]. However, the big picture for the effect of changes in treatment of PAD was not drawn.

In this issue of *Atherosclerosis,* Agnelli et al. [8], accepted the challenge. The authors report results in terms of morbidity and mortality in PAD patients of a meta-analysis with approximately 570,000 patients with about 855,000 person-years out of 124 eligible studies from 2003 to 2017. They built the bridge between the vast amount of heterogeneity between RCTs (only 15%, n = 19) and observational studies. Unfortunately, but expected, PAD and outcome definitions highly differed between the groups (ABI < 0.9 *vs* IC; differing CLI criteria). Nevertheless, the authors made remarkable findings with event rates comparable to other atherosclerotic diseases with especially high event-rates in the CLI branch. All-cause and cv mortality rates in patients with an ABI < 0.9 were 113 and 39 per 1000 person-years, respectively, and for CLI 183 and 81 per 1000 person-years, respectively. In fact, the overall event-rate of 113 per 1000 person-years surpasses comparable coronary heart disease data [9,10]. Interestingly, trials starting from 2008, after the publication of the TASC II guidelines [11] and the 2005 ACC/AHA PAD guidelines [12], had lower cv event-rates (36 *vs* 46 per 1000 person-years) than trials before 2008. Unfortunately, the authors did not provide data on changes of secondary prevention medication with the 2008 threshold, while generally there was need of improvement, especially with only 55% of statin intake in the CLI subgroup (see Table 1). Apart from the vast number of patients, the observation period of approximately 1.3 years per patient remains short for outcome analyses. In a subgroup analysis, the all-cause mortality event-rate for studies with a long observation period (> 1.3 years) was lower than in those with a short observation period (< 1.3 years) (Appendix 4b). Since 85% of these studies were of observational character, lost to follow-up might have provoked this disparity. Furthermore, a wide range of 25–468 events per 1000 person-years was found in the CLI group and CLI patients had less outcome events in the RCT than in the observational trial branch. Apart from the expectable better-than-real-life situation in RCTs, these disparities indicate a proportion of misdiagnosed diabetic foot patients, which have worse outcome than CLI patients, in the CLI branch. Interestingly, stroke rates were not higher in CLI compared to PAD patients. However, one should be cautious with this result, since only a small proportion of less than 15% of the analysed studies reported stroke events and the authors did not provide the actual sample size of this sub-analysis.

So, what can we learn from the biggest up to date picture for PAD?

In fact, apart from the problems derived from the vast heterogeneity of the studies analysed and the short observation period of approximately 1.3 years, the presented data teaches us the future direction for the clinical pathway. All obstacles from differing diagnostic assessment and definitions to unmet treatment goals of PAD/CLI result in higher mortality event-rates than in comparable atherosclerotic diseases of different vascular beds.

Thus, we as a community should tackle this problem and once again raise awareness of PAD in the clinical setting. Furthermore, the demonstrated rates of secondary prevention therapy have a scope of improvement, especially in CLI patients. Thus, with the implementation of recently proposed stricter treatment goals [7,13] future trials might report smaller event-rates both in RCTs as well as observational trials.

In summary, the results of Agnelli et al. can be seen as a challenge for optimisation both of diagnostic criteria and therapy of PAD in future

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trials.

Declaration of competing interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

References

[1] M.H. Criqui, V. Aboyans, Epidemiology of peripheral artery disease, Circ. Res. 116 (2015) 1509–1526.

[2] F.G. Fowkes, D. Rudan, I. Rudan, et al., Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis, Lancet 382 (2013) 1329–1340.

[3] A.T. Hirsch, M.H. Criqui, D. Treat-Jacobson, et al., Peripheral arterial disease detection, awareness, and treatment in primary care, JAMA 286 (2001) 1317–1324.

[4] J.W. Eikelboom, S.J. Connolly, J. Bosch, et al., Rivaroxaban with or without aspirin in stable cardiovascular disease, N. Engl. J. Med. 377 (2017) 1319–1330.

[5] M.S. Sabatine, R.P. Giugliano, A.C. Keech, et al., Evolocumab and clinical outcomes in patients with cardiovascular disease, N. Engl. J. Med. 376 (2017) 1713–1722.

[6] A.T. Hirsch, Z.J. Haskal, N.R. Hertzer, et al., ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American association for vascular surgery/society for vascular surgery, society for cardiovascular angiography and interventions, society for vascular medicine and biology, society of interventional radiology, and the ACC/AHA task force on practice guidelines (writing committee to develop guidelines for the management of patients with peripheral arterial disease) endorsed by the American association of cardiovascular and pulmonary rehabilitation; national heart, lung, and blood institute; society for vascular nursing; TransAtlantic inter-society consensus; and vascular disease foundation, J. Am. Coll. Cardiol. 47 (2006) 1239–1312.

[7] V. Aboyans, J.B. Ricco, M.E.L. Bartelink, et al., 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European society for vascular surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries endorsed by: the European stroke organization (ESO)the task force for the diagnosis and treatment of peripheral arterial diseases of the European society of cardiology (ESC) and of the European society for vascular surgery (ESVS), Eur. Heart J. 39 (2018) 763–816.

[8] Agnelli, Morbidity and Mortality Associated with Atherosclerotic Peripheral Artery Disease: a Systematic Review, Atherosclerosis, 2019 (please check correct citation).

[9] M.R. Carnethon, M.L. Biggs, J. Barzilay, et al., Diabetes and coronary heart disease as risk factors for mortality in older adults, Am. J. Med. 123 (2010) 556.e551-559.

[10] L. Whiteley, S. Padmanabhan, D. Hole, et al., Should diabetes be considered a coronary heart disease risk equivalent?: results from 25 years of follow-up in the Renfrew and Paisley survey, Diabetes Care 28 (2005) 1588–1593.

[11] L. Norgren, W.R. Hiatt, J.A. Dormandy, et al., Inter-society consensus for the management of peripheral arterial disease (TASC II), J. Vasc. Surg. 45 (Suppl S) (2007) S5–S67.

[12] A.T. Hirsch, Z.J. Haskal, N.R. Hertzer, et al., ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American association for vascular surgery/society for vascular surgery, society for cardiovascular angiography and interventions, society for vascular medicine and biology, society of interventional radiology, and the ACC/AHA task force on practice guidelines (writing committee to develop guidelines for the management of patients with peripheral arterial disease): endorsed by the American association of cardiovascular and pulmonary rehabilitation; national heart, lung, and blood institute; society for vascular nursing; TransAtlantic inter-society consensus; and vascular disease foundation, Circulation 113 (2006) e463–654.

[13] F. Mach, C. Baigent, A.L. Catapano, et al., 2019 ESC/EAS Guidelines for the Management of Dyslipidaemias: Lipid Modification to Reduce Cardiovascular Risk, European heart journal, 2019.

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