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Predicting incident peripheral artery disease and critical limb ischemia: Feeling the pulse!

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The physician cannot prescribe by letter, he must feel the pulse.

Lucius Annaeus Seneca[1]

Peripheral artery disease (PAD) is a common and complex cardiovascular condition ranging from asymptomatic atherosclerosis to limb-threatening ischemia requiring emergency treatment.[2,3] Despite remarkable improvements in primary and secondary prevention, as well as endovascular and surgical therapy, PAD and its most dreadful presentation, i.e. critical limb ischemia (CLI), continue to take a heavy morbidity and mortality toll worldwide.[3] Accordingly, more intense preventive efforts accompanied by refined predictive models continue to be encouraged.[2] In addition, a key peculiarity of PAD is that it shares a large part of its pathophysiology (e.g. the interplay between inflammation, lipid metabolism and rheology) with coronary artery disease (CAD) and cerebro-vascular disease (CVD) and thus its appropriate management provides benefits for CAD and CVD as well.[4] On the other hand, patients with poorly managed or overlooked PAD often have adverse events which depend on CAD or CVD progression, before or concomitantly with PAD progression.[2,3]

Yet, PAD is a heterogeneous disease, which may affect large vessels such as abdominal aorta, iliac arteries, femoral arteries and popliteal arteries, as well as infra-popliteal vessels (i.e. anterior tibial arteries, posterior tibial arteries, and fibular arteries).[5] Typically, but not invariably, chronic PAD affecting the most proximal vessels is either asymptomatic or leads to claudication, whereas chronic PAD affecting infrapopliteal arteries may be asymptomatic or lead to pain at rest or tissue loss.[6] Conversely, atherothrombotic progression of PAD may lead to acute limb loss irrespective of its localization. In light of these anatomic peculiarities, another complicating issue regarding PAD is the approximate diagnosis in clinical practice and research, with ankle-brachial index (ABI) still often used for diagnostic purposes rather than screening only, despite its inaccuracy in comparison to duplex ultrasound, computed tomography, or magnetic resonance imaging.[7]

Given these premises, when should PAD be suspected or aggressive preventive measures be considered? Several studies have tried to identify predictors of PAD (Figure 1), both as incident and prevalent cases.[8–15] Interestingly, several factors may predict this condition, in keeping with the well-known multifactorial pathophysiology of atherosclerosis.[4] Yet, it is evident that, while some risk factors cannot be modified (e.g. age or gender), other are eminently sanctionable (e.g. tobacco cigarette smoking), with a risk reduction strategy or aggressive medical therapy.[16–17] In particular, clinicians have proved well versed in the last decades in managing arterial hypertension, which has detrimental impact on PAD as well as CAD and CVD. Despite these successes, we still need to refine our understanding and management of hypertension.[18]

This issue of the Journal provides indeed a landmark analysis of the Atherosclerosis Risk in Communities (ARIC) Study, detailing long-term follow-up (>20 years) of subjects devoid of PAD at enrolment, and in

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Feature	Study							
	Khan (2006)	Bendermacher (2007)	Cournot (2007)	Makdisse (2007)	Daskalopoulou (2008)	Suominen (2008)	Zhang (2016)	Tunstall-Pedoe (2017)
Age		+					+	+
Family history								+
African-American race							+	
Male gender							+	+
Socioeconomic status								+
Hypertension		+		+				+
Smoking		+		+		+	+	+
Diabetes mellitus					+			
Dyslipidemia					+			
Renal failure				+	+	+		+
CAD						+		
C-reactive protein					+			+
NT-pro-BNP								+
Femoral bruit	+		+					
Cool skin	+							
Pulse abnormality	+		+	+				
Claudication	+			+				
Femoral plaque			+					

Figure 1. Selected studies on predictors of incident and prevalent peripheral artery disease (+ indicates a significant independent association). CAD: coronary artery disease; NT-pro-BNP: N-terminal pro-brain natriuretic peptide.

whom the most recent (2017) American Heart Association (AHA)/American College of Cardiology (ACC) Hypertension Guideline definitions were applied.[19,20] Specifically, Lu et al.[19] distinguished *normal blood pressure* (BP, defined as systolic blood pressure [SBP] < 120 Hg, diastolic blood pressure [DBP] < 80 mm Hg, and no anti-hypertensive medications), from *elevated BP* (defined as SBP 120–129 mm Hg and DBP < 80 mm Hg), *stage 1 hypertension* (defined as SBP 120–129 mm Hg and DBP 80–89 mm Hg), and *stage 2 hypertension* (defined as SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg). They further characterized incident PAD as hospitalizations or revascularizations due to this condition or to CLI, rather than simply abnormal ABI or anatomic evidence of PAD at non-invasive or invasive imaging, and carried out careful unadjusted and multivariable adjusted analyses to clarify the impact of different BP categories on subsequent risk of PAD or CLI. They clarify that, at odds with current guideline consensus, elevated BP had an impact on the risk of PAD similar to that of stage 1 hypertension, at least up to 15–18 years of follow-up. Intriguingly, relatively high SBP seemed to confer a higher risk than relatively high DBP, especially when both BP measures were simultaneously considered. Finally, they highlighted that the risks conferred by elevated BP, stage 1 hypertension, and stage 2 hypertension were significantly greater in patients already on anti-hypertensive medications than in naïve subjects. While this may seem counterintuitive, it can actually be easily explained by selection bias or, more likely, resistant hypertension features.

Despite this work strengths, we should be aware that this study is quite old, at least as far as enrolment is concerned, and thus may not reflect current state-of-the-art practice in prevention, diagnosis, and management. This holds true for PAD, but also for hypertension itself. In addition, only PAD events were collected, whereas it would have been important to highlight also the impact of BP on other crucial events such as death, myocardial infarction, stroke, and heart failure, just to name a few, as well as on asymptomatic PAD (e.g. defined at non-invasive imaging).

In conclusion, feeling the pulse of our patients, either in the prediction of upcoming PAD, or more banally to diagnose it, remains a crucial part of our cardiovascular practice. Accordingly, BP management must be proactive, remembering that in most cases the lower the BP (especially SBP) the better, as long as this intensive anti-hypertensive therapy is well tolerated.

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