

YOUNG INVESTIGATORS:

Vascular ageing biomarkers: are we ready for the hypertension guidelines?

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Vascular ageing refers to the age-related deterioration in vascular structure and function and is accelerated in the presence of cardiovascular risk factors. In an optimally functioning cardiovascular system, the elastic properties of the large arteries (i.e. aorta) ensure that pulsations in pressure and flow generated by left ventricular contraction are dampened so that less pulsatile pressure/flow are delivered at the microvascular level. However, the cushioning (elastic) properties of the large arteries are progressively lost over time. While age-related arterial damage typically appears in the fifth decade of life, there is wide variability between individuals, with some displaying early vascular ageing. This has led to the concept that vascular age, as opposed to chronological age, may be better related to the prognosis of CVD¹, is the driving force behind age-related chronic disease in multiple organs, and is responsible for the largest proportion of disease burden worldwide².

Among vascular ageing biomarkers, one of the most robust and promising is arterial stiffness (a proxy for arteriosclerosis). Carotid to femoral pulse wave velocity (PWV) is currently the gold standard non-invasive method for determining large artery stiffness in a clinical setting. Many studies have shown that the stiffness of the large arteries is related to elevated CVD risk in adults, independently of traditional cardiovascular risk factors³. In an individual participant meta-analysis involving data from 17 635 participants, Ben-Shlomo et al. showed that after adjusting for age and sex, a 1-SD difference in log-transformed carotid to femoral PWV was associated with a 35% increased risk of future CVD events over the 5-year follow-up

period, independent of cardiovascular risk factors and medications⁴. Furthermore, the addition of carotid to femoral PWV to traditional Framingham risk factors in a group at intermediate risk of CVD, improved risk stratification by 13%⁴.

While arterial stiffness is an important component, other measures depicting the atherosclerotic process of vascular ageing at various stages, such as carotid intima media thickness and plaque, coronary calcium score and endothelial function are available. Given that factors influencing vascular age are numerous and their impact on vascular health varies between individuals, a direct, non-invasive assessment of arterial health status is advisable. However, recommendations for the assessment of vascular aging is strikingly underrepresented in the current guidelines on hypertension and CVD prevention from international societies. Carotid ultrasound, ankle-brachial index and CT coronary artery calcium (CAC) score are recommended according to the European Society of Cardiology (ESC) guidelines for cardiovascular prevention because of their reclassification potential in addition to classical cardiovascular risk scores⁵, whereas the American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend only CAC⁶.

However, these biomarkers only depict the atherosclerosis phenomenon, which is only one side of the coin. Furthermore, CAC require a CT scan, thus is not feasible for large population screening in low-resource settings and carries inherent risk.

When turning to guidelines for the management of hypertension, according to the 2007 and 2013 ESC/European Society of Hypertension (ESH) guidelines, quantification of total cardiovascular risk must include an investigation of subclinical vascular organ damage. However in the 2018 guidelines, the systematic use of PWV (as well as carotid ultrasound and ankle brachial index) is not recommended, despite being mentioned in the hypertension-associated organ damage list⁷, and evidence confirming PWV ability to reclassify risk is now available⁴. Finally, the recent ISH guidelines recommend the measurement of PWV only in specific cases, such as isolated systolic hypertension⁸. Indeed, in the past years a number of vascular aging biomarkers (such as PWV) have been shown to have prognostic significance and simple, low-cost, fully non-invasive devices for measuring such biomarkers are increasingly available. However, studies assessing the clinical value of a reduction in PWV via treatment remain scarce.

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The recently commenced European Cooperation in Science and Technology Action VascAgeNet ("Network for Research in Vascular Ageing", CA18216, www.vascagenet.eu) aims to directly address these unmet needs limiting the measurement of vascular age in routine clinical practice. The purpose of the COST Action is to bring together industry, basic and clinical science to foster innovation⁹ and to refine the approaches for assessing vascular ageing, to harmonize existing data and knowledge and to promote the importance of monitoring vascular age to improve clinical outcomes¹⁰. Furthermore, the COST Action will promote large-scale, registry-based interventional studies, aimed at assessing the clinical value of the use of vascular aging biomarkers as targets for treatment. It is hoped that through this Action and by addressing these limitations, definitive recommendations for the measurement of vascular age in clinical practice can be incorporated into future guidelines for hypertension and CVD management, ultimately contributing to a reduction in CVD burden globally.

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