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EDITORIAL COMMENT

Personalizing Cardiovascular Disease Risk Assessment

Is it Time to Forget About Chronologic Age?*

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It is commonly said that "age is just a number," and chronologic age, calculated as the time elapsed from birth, has been the primary way to define an individual's age. However, this method fails to account for the complex and diverse processes of aging. Indeed, a person's genetics along with their diet, lifestyle, and cumulative exposure to risk factors leads to significant heterogeneity in biologic age for persons of the same chronologic age. This creates a problem for cardiovascular risk calculators such as the Pooled Cohort Equation (PCE), because chronologic age is the most heavily weighted variable. Nearly all adults younger than 40 years have a low 10-year predicted risk of atherosclerotic cardiovascular disease (ASCVD), while most men >60 and women >65 years of age have at least an intermediate 10-year ASCVD risk from 7.5% to 20%, regardless of their traditional risk factor burden.

The shortcomings of chronologic age have led to an increased recognition that other measures are needed to better classify an individual's biologic age and ASCVD risk. Genetic biomarkers of DNA methylation and telomere length have been linked to acceleration of the aging processes, but the cost of testing and expertise needed for interpretation of the results limit their widespread use in clinical practice.[1]

Interestingly, even a subjective estimation of an individual's perceived age provides significant insight into their biologic age and survival.[2] More direct quantification of arterial or vascular aging with the use of coronary artery calcium (CAC) scoring or noninvasive markers of arterial stiffness such as pulse-wave velocity (PWV) also better classify biologic age, which in turn improves ASCVD risk stratification relative to models that rely on chronologic age and may provide a more accurate and personalized estimate of ASCVD risk.[3,4]

With the basic concept that pulse waves travel faster in stiffer arteries, PWV is a noninvasive measure of arterial stiffness that is strongly linked to increased biologic age. Compared with measuring systolic and diastolic blood pressure, measuring PWV provides distinct information on vascular health that is specifically related to vascular compliance and distensibility and is an early marker of poor vascular health, even before the development of hypertension. PWV is also strongly associated with cardiovascular outcomes and improves risk prediction beyond traditional cardiovascular risk factors, with a 30% increased risk for cardiovascular disease (CVD) for every 1 standard deviation higher PWV.[5] As such, PWV is one simple method to improve the measurement of biologic age.[4]

In this issue of *JACC: Asia*, Zuo et al[6] conducted an analysis to validate brachial-ankle (ba) PWV-measured vascular age (VA) using the method that Bruno et al developed from carotid-femoral (cf) PWV measured in a cohort of European participants aged 61-88 years. The prospective registry in the present study included 20,917 middle-aged adults (73% men) from the Kailuan community in Tangshan City, China, aged 40-60 years without a history of myocardial infarction or stroke. VA was calculated with the use of multivariable regression modeling, and patients were grouped according to the difference between their chronologic age and calculated VA, termed Δ-age.

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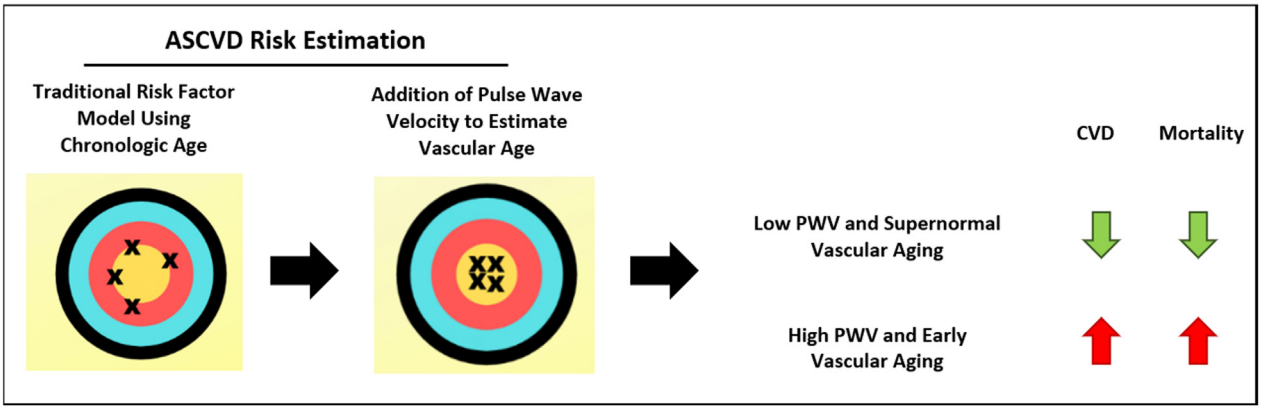
FIGURE 1 **Impact of PWV of ASCVD Risk Prediction**



Incorporation of pulse-wave velocity (PWV) to estimate vascular age and improve cardiovascular risk stratification. Thick black arrows indicate subsequent effects of adding PWV to estimate vascular age, green arrows indicate decreased cardiovascular disease (CVD) and mortality, and red arrows indicate increased CVD and mortality. ASCVD = atherosclerotic cardiovascular disease.

Participants with early VA were defined as having the 10th percentile of Δ-age (VA 5.7 years > chronologic age) and those with supernormal VA, or healthier than expected VA, were in the 90th percentile of Δ-age (VA 6.2 years < chronologic age). The rest of the subjects were defined as the normal VA category. The primary outcome was a composite of myocardial infarction, hospital admission for heart failure, and stroke.

Participants with early VA were significantly younger than those with supernormal VA by an average of 16 years and had a significantly higher adjusted risk of cardiovascular events (HR: 1.90; 95% CI: 1.22-2.95; $P < 0.01$). However, there was no significant difference in all-cause mortality (HR 1.30; 95% CI: 0.63-2.68). Participants with supernormal VA had a strong, inverse association with both all-cause mortality (HR: 0.65; 95% CI: 0.42-0.99; $P < 0.01$) and cardiovascular outcomes (HR: 0.52; 95% CI: 0.32-0.86; $P < 0.01$). Every 1 year of VA lower than chronologic age was associated with 26% and 18% reductions in the age- and sex-adjusted risk of cardiovascular events and all-cause mortality, respectively. Furthermore, adding baPWV into conventional risk models significantly improved model fit (difference in C-statistic for all-cause mortality = 0.048; 95% CI: 0.033-0.062; $P < 0.001$).

Strengths of this study include the large sample size and use of a previously developed VA model. In addition, this investigation found that baPWV measured in a Chinese population of middle-aged adults compared favorably with VA derived using the criterion standard of cfPWV measured among a group of older European participants, demonstrating similar results between the 2 methods of measuring PWV across ethnicities. The low percentage of women prevented the development of a sex-specific VA equation, which is an important limitation given the known differences between men and women in the temporal development and progression of atherosclerosis and CVD as well as arterial stiffness. Additional limitations include the fact that PWV is still primarily used as a research tool and reimbursement is not covered by Medicare. Furthermore, other commonly used and guideline-recommended tests, such as CAC score, can be used to estimate biologic age, which limits clinician enthusiasm for performing PWV screening.

Though not directly evaluated by Zuo et al,[6] discussing biologic age with patients rather than a 10-year ASCVD risk estimate may be a more intuitive method to communicate risk that may better motivate actionable behavioral and lifestyle changes.[3] Findings from this study are consistent with other analyses demonstrating that higher PWV is associated with adverse CVD outcomes and can improve ASCVD risk prediction beyond traditional risk factors (**Figure 1**). The SPARTE (Strategy for Preventing Cardiovascular and Renal Events Based on Arterial Stiffness) trial examined the utility of a blood pressure-lowering intervention to normalize cfPWV among 536 adults with hypertension.[7] The trial failed to meet its primary endpoint (HR: 0.74; 95% CI: 0.40-1.38; $P = 0.35$), a composite outcome of cardiovascular events, chronic

kidney disease, and sudden death, although the trial was underpowered due to low recruitment. There was a significantly greater reduction in systolic blood pressure (−1.08 mm Hg/y vs −0.10 mm Hg/y; $P = 0.001$) and less increase in PWV (0.06 m/s per year vs 0.2 m/s per year; $P = 0.012$) for participants in the PWV group compared with usual care.

The findings by Zuo et al[6] provide additional evidence for the importance of incorporating better measures of biologic age to improve and personalize CVD risk prediction, given the difficulties in quantifying differences in diet, lifestyle, and genetics across diverse Asian populations and other racial/ethnic groups. Quantification of biologic age could be used as a risk enhancer to provide a better estimate of ASCVD risk for Asian people, because the PCE does not have specific risk estimates for this group.

The results of this study show us that the answer to the question "Is (chronologic) age really just a number?" is a resounding "yes" and that it may be time to use biologic age and forget about chronologic age when we want to provide a more accurate ASCVD risk estimate. Using PWV-quantified VA or other measures of biologic age can provide additional information to better risk-stratify patients that may be more easily interpreted by patients, potentially leading to better adherence of behavioral and lifestyle goals along with more appropriate allocation of prevention therapies.

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