

EDITORIAL

Transitioning the Menopause

A Stiff Challenge

Carmel M. McEniery

The menopause represents a significant, transitional phase in the lives of women, during which dynamic changes in physiology, metabolism, and general physical and mental well-being occur. One of the most significant impacts of the menopause is on the risk of future cardiovascular disease (CVD), currently the leading cause of death in adults.¹ Indeed, although CVD risk increases with age in both men and women, menopause is associated with an accelerated increase in the risk of CVD events in women,¹ although our understanding of the factors mediating this change in risk remains incomplete, and a key women's health objective.

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Recent attention has focused on changes in vascular structure and function during the menopause transition, as potential mediators of the increased risk of future CVD. In this regard, large artery stiffening may be particularly important, because with stiffening, the aorta and other large elastic arteries lose their protective ability to buffer the cyclical changes in blood pressure resulting from cardiac ejection. This loss of buffering has a number of adverse consequences,² including transmission of potentially damaging pulsatile forces to high-flow–low-resistance organs such as the brain and kidneys.³ Indeed, carotid-femoral pulse wave velocity (cfPWV)—a robust measure of aortic stiffness—is now widely recognized as an important, independent determinant of cardiovascular outcomes,² as illustrated by a recent large individual participant level meta-analysis of prospective studies,⁴ where a 1-SD increase in cfPWV was associated with a 43% increase in the risk of CVD events.

Evidence from cross-sectional studies demonstrates that large artery stiffness is increased in postmenopausal versus premenopausal women, even after adjustment for the confounding influences of age, blood pressure, and other traditional CVD risk factors.^{5,6} More recently, data from the longitudinal SWAN Heart Study (Study of Women Across the Nation)—an ancillary study of the larger SWAN study⁷—demonstrated that progression of cfPWV was greater in those women who transitioned through menopause during the study follow-up compared with those women who remained premenopausal or were already postmenopausal,⁸ indicating that the menopause transition may be a critical time in which arterial stiffening accelerates, potentially translating to the observed future increased risk of CVD.

In this issue of the journal, Samargandy et al⁹ extend on these recent findings, presenting further analyses from a biracial sample of women from the SWAN Heart study examining when, within the menopause transition, significant changes in arterial stiffening occur. In all, 339 women contributed 537 observations, with a mean±SD follow-up of 2.3±0.5 years. The authors used a statistical modeling approach to calculate annual changes in cfPWV and how these changes differed across 3 specific time segments related to the final menstrual period (FMP). Overall, cfPWV increased significantly within 1 year of the FMP, after adjustment for covariates including age, standard CVD risk factors, and levels of the female sex hormones, estradiol and FSH (follicle-stimulating hormone). Intriguingly, the accelerated rise in cfPWV occurred earlier in black women than in white women, suggesting a different trajectory of arterial stiffening during the menopause transition in black women, which may, in turn, impact on their trajectory of future CVD risk.

Key Words: Editorials ■ aorta ■ humans ■ perimenopause ■ vascular stiffness ■ women's health

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For Sources of Funding and Disclosures, see page 851.

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Arterioscler Thromb Vasc Biol is available at www.ahajournals.org/journal/atvb

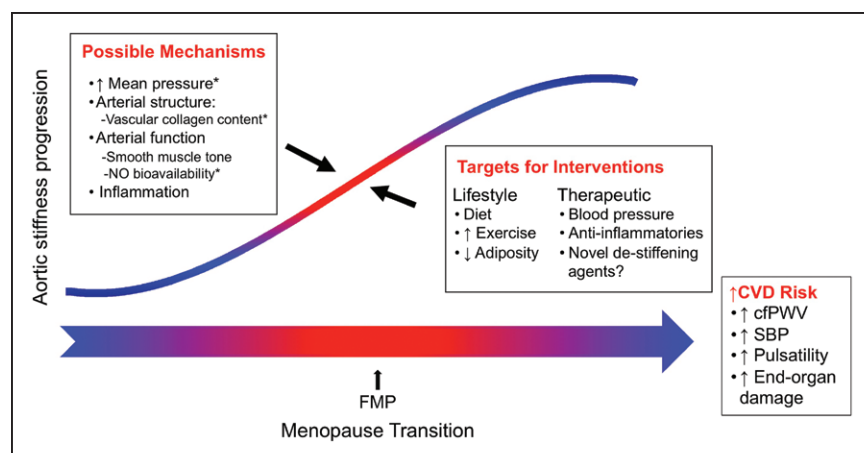


Figure. Accelerated arterial stiffening during the menopause transition: possible mechanisms and targets for interventions.

CfPWV indicates carotid-femoral pulse wave velocity; CVD, cardiovascular disease; FMP, final menstrual period; and SBP, systolic blood pressure. *Refers to mechanisms where evidence for racial differences exists.

These data from the SWAN Heart Study are particularly interesting because they suggest that efforts to understand, and intervene on, the mechanisms underlying accelerated arterial stiffening could be focused on a relatively narrow window of time within the menopause transition (Figure), allowing investigators the opportunity to maximize the efficient use of time and resources. The potential mechanisms underlying accelerated arterial stiffening during the menopause transition have been reviewed extensively elsewhere^{10–12} and include, but are not limited to, effects related to elevated vessel distending pressure (ie, mean arterial pressure)—a key determinant of arterial stiffness,¹³ where higher levels of blood pressure may drive further arterial stiffening, resulting in a vicious cycle¹⁴; changes in arterial wall structure including increased vascular collagen content^{11,15}; changes in vascular smooth muscle tone and, in particular, NO bioavailability^{6,10}; and inflammation,^{11,12} all of which are linked, to some extent, with estrogen deficiency. There is also variable evidence that black individuals have reduced NO bioavailability,¹⁶ and elevated vascular collagen content¹⁵ and blood pressure,¹⁷ which may help to explain the different trajectory of stiffening observed in black women in the SWAN Heart Study.⁹

The findings of Samargandy et al⁹ are certainly intriguing and worthy of further investigation. Indeed, they represent an exciting opportunity for detailed investigations of the mechanisms driving accelerated arterial stiffening in women transitioning through menopause and especially in black women. They also highlight an ideal time frame within the menopause transition for targeting specific destiffening interventions, such as lifestyle modification and risk factor reduction, as suggested by Samargandy et al.⁹ Indeed, aerobic exercise training improves arterial stiffness in postmenopausal women^{5,6} but may be even more effective when undertaken during the menopause transition. As yet, there are no specific destiffening drug therapies available, but the future development and application of these could be transformative. In the meantime, reducing arterial stiffness via blood pressure reduction is also likely to be helpful. Transitioning the menopause

represents a stiff challenge for women, but an important window of opportunity now exists for focused, translational research which could, ultimately, change the trajectory of future CVD risk in women.

ARTICLE INFORMATION

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Sources of Funding

This work was funded, in part, by the National Institute for Health Research (NIHR) Cambridge Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NIHR.

Disclosures

None.

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