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COMMENT

Is carotid arterial stiffness a therapeutic target of statin therapy?

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Arterial stiffness is a general term used to describe the rigidity of the arterial walls. Several indices of arterial stiffness have been developed and validated thus far, and each index provides a different measure of systemic, segmental, or local arterial stiffness [1]. Systemic arterial stiffness can only be estimated by using models of the circulation. In contrast, segmental or local arterial stiffness can be directly measured at various sites along the arterial tree. Pulse wave velocity (PWV) reflects segmental arterial elasticity. Measurement of PWV in a specific vessel segment, such as carotid-femoral PWV and brachial-ankle PWV, has been used for the assessment of segmental arterial stiffness. Measurement of PWV is the most widely used method for the assessment of arterial stiffness in clinical practice. Local arterial stiffness of superficial arteries, such as the carotid artery, femoral artery and brachial artery, can be determined by direct measurement of the vessel diameter changes in diastole and systole throughout the cardiac cycle using ultrasound techniques. Several measures, such as compliance, distensibility and elastic modulus, have been developed for describing local arterial stiffness. Compliance is defined as the ratio of any volume change for a given pressure change and is an inverse measure of arterial stiffness (the higher the compliance, the lower the arterial stiffness). Distensibility is defined as the relative change in arterial lumen diameter or lumen area for a given pressure change. Distensibility is similar to compliance but is a more useful measure when arteries of different sizes are compared across the arterial tree. The elastic module is defined as the pressure change for a theoretical 100% increase in diameter, and it is an inverse measure of distensibility (the higher the elastic module, the higher the arterial stiffness). Young's elastic modulus (YEM) is a commonly used measure of the elastic properties of the arterial wall material that takes the wall thickness into account. YEM is defined as the wall tension per centimeter of wall thickness for a 100% increase in diameter.

Increased arterial stiffness per se may contribute to the progression of end-organ damage and the development of cardiovascular events. The conduit arteries play an important role in buffering the pulsatile flow generated by cardiac contractions and converting the pulsatile flow into a steady flow, which is the so-called "cushioning effect". Attenuation of the cushioning effect of large arteries as a result of increased arterial stiffness therefore has deleterious effects on the cardiovascular system, including increased cardiac afterload, impaired coronary blood flow, and functional decline in high-blood flow organs such as the brain and kidney through microvascular damage, which can lead to end-organ damage and cardiovascular complications. Carotid arterial stiffness may play a certain role in downstream brain circulation. Although the exact role of carotid arterial stiffness in the development of cerebrovascular disease is still under investigation, one proposed mechanism underlying the direct association between carotid arterial stiffening and cerebrovascular disease is that attenuation of the cushioning effect of the carotid artery may result in more continuous perfusion, rather than pulsatile perfusion, which can lead to an increase in flow load on the cerebral parenchyma. Since the overall impedance of the cerebral parenchyma is low, the increased blood flow can penetrate deep into the cerebral arterial microvasculature and cause cerebral parenchymal damage, including hemorrhage, ischemia, and other markers of small vessel disease. This end-organ damage to the

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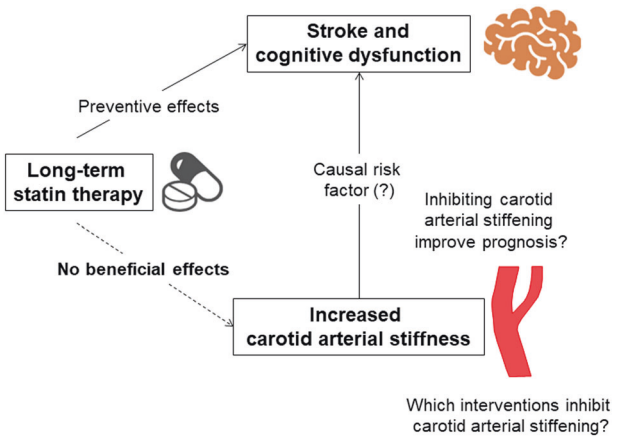

Fig. 1 Associations of long-term statin therapy with carotid arterial stiffness and cerebrovascular disease

brain parenchyma can manifest as stroke, cognitive decline, dementia, or cerebral small vessel disease detected by brain imaging studies [2]. Therefore, assessment of carotid arterial stiffness is expected to provide additional information for cardiovascular risk assessment independent of traditional cardiovascular risk factors and aortic stiffness. Indeed, the results of a meta-analysis have shown that increased carotid arterial stiffness is significantly associated with an increased risk of stroke independent of cardiovascular risk factors and aortic stiffness [3].

Lifestyle modifications and treatment of cardiovascular risk factors can inhibit the progression of arterial stiffness, leading to improvement in cardiovascular prognosis. Statins are the most widely used cholesterol-lowering agents. Statins may exert additional beneficial effects on the cardiovascular system beyond lowering low-density lipoprotein cholesterol (LDL-C) levels, and these include decreasing oxidative stress and inflammation, enhancing the stability of atherosclerotic plaques, and inhibiting the thrombogenic response. Therefore, statin treatment has been expected to inhibit the progression of arterial stiffness by exerting their short-term and long-term beneficial effects on vascular remodeling by reducing vascular smooth muscle tone and changing the lipid content and composition within the vessel wall. Although the association between arterial stiffness and statin therapy has not been fully elucidated, the results of a meta-analysis, in which the short-term effect of statin therapy on aortic stiffness was investigated, showed that aortic PWV was significantly lower in subjects with statin treatment than in subjects without statin treatment, suggesting that short-term statin treatment can improve aortic stiffness [4]. However, there is little information on the long-term effect of statin treatment on local arterial stiffness. In the current issue of *Hypertension Research*, Anatoliy et al. reported the results of an investigation of the long-term effect of statin treatment on carotid arterial stiffness by examining the associations of indices of carotid arterial stiffness, including distensibility coefficient (DC) and YEM, with the duration of statin therapy, intensity of statin therapy, and LDL-C trajectories over 10 years [5]. Data were derived from a post hoc analysis of the Multi-Ethnic Study of Atherosclerosis (MESA), a population-based cohort of subjects aged 45 to 84 years who were free of known cardiovascular disease at baseline. The authors reported that there was no significant association of the percent change in DC or YEM with the duration of statin therapy, intensity of statin therapy, or LDL-C trajectories over the 10-year follow-up period. These findings suggest that long-term statin treatment has no inhibitory effect on the progression of carotid arterial stiffness regardless of statin treatment duration, statin intensity, or LDL-C control. Given that statin therapy can reduce the risk of stroke [6], the results of the study suggest that the beneficial effect of statin treatment on stroke prevention is not due to the modification of carotid arterial stiffness.

Figure 1 shows the associations of long-term statin therapy with carotid arterial stiffness and cerebrovascular disease. The results of the present study will help us to better understand the pathophysiological mechanisms underlying the associations between carotid arterial stiffness, stroke, and statin treatment. However, several issues remain to be clarified. It has not been determined whether inhibiting the progression of carotid arterial stiffness reduces the risk of stroke. In addition, it is unclear which interventions, other than lowering blood pressure, inhibit the progression of carotid arterial stiffness. To answer these questions, standardization of the measurement method for carotid arterial stiffness and establishment of diagnostic criteria for carotid arterial stiffening are necessary. Further studies on the role of carotid arterial stiffness as a vascular marker may further enhance the clinical implications of the present study.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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