Editorial

# Dual benefits of renin-angiotensin-aldosterone blockade: lowering the blood pressure and de-stiffening the arteries

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Stiffening of arteries is due to the loss of elasticity and compliance in the diseased media (1). Arterial stiffness raises systolic blood pressure (BP) and further increases left ventricular (LV) afterload and myocardial oxygen demand (2). Arterial stiffness also causes decreased diastolic BP and subsequent reduction of coronary perfusion (3). The elevated systolic BP and decreased diastolic BP together result in higher pulse pressure, which leads to fragmentation of elastin in the aorta and damages high-flow, low-resistance cerebral and renal circulation as well. Along the stiffened arterial trees, pulse wave propagation accelerates and wave reflection from the periphery towards the heart occurs earlier and more proximally, so that the central BP is increased (3). The hemodynamic changes result in LV hypertrophy, diastolic dysfunction and myocardial ischemia, which amplify the risk of cardiovascular events, including coronary artery disease, heart failure, and stroke. For patients with essential hypertension, arterial stiffness independently predicts cardiovascular and all-cause mortalities (4).

Aging and elevated BP are the two major factors contributing to increased arterial stiffness. Structurally, aging and increased circumferential wall stress result in degeneration of medial elastic fibers in central arteries (5). Increased collagen deposition and cross-linking with advanced glycation end-products further stiffen the extracellular matrix of the arteries (6). In our recent studies, excess aldosterone is associated with increased carotid intima-media thickness (cIMT) and impaired smooth muscle relaxation, suggesting renin-angiotensin-aldosterone system (RAAS) activation contributes to the development of arterial stiffness (7,8).

It is not practical to obtain vascular specimens for structural examination and measurement of stiffness in daily practice. Several non-invasive methods have been used to assess arterial stiffness. One of most commonly used parameter is pulse wave velocity (PWV) and carotid-femoral PWV is the gold standard (9). PWV reflects segmental arterial elasticity between two sites, and a higher PWV value indicates stiffer artery. Previous studies have demonstrated the usefulness of PWV in prediction of cardiovascular events and risk stratification (1,2).

Arterial stiffness is reduced as the arterial BP is lowered by treatment and it is intriguing if anti-hypertensive medication has additional benefit to arterial stiffness *per se* (10). Previous meta-analysis by Ong *et al.* revealed that angiotensin-converting enzyme inhibitors (ACEIs) are more effective in reducing carotid-femoral PWV than calcium channel blocker (CCB) and placebo over short-term (less than 4 weeks) (11). However, four classes of anti-hypertensives (ACEI, CCB, beta-blocker, and diuretics) had similar effects to reduce carotid-femoral PWV in long-term (4 weeks to 6 months) trials (11). In another meta-analysis by Shahin *et al.*, they compared the effects between ACEI and other four classes of anti-hypertensives [angiotensin receptor blocker (ARB), CCB, beta-blocker, and diuretics] in reducing carotid-femoral PWV (data from 9 trials) and augmentation index (AI) (data from 7 trials) (12). In PWV analysis, ACEIs insignificantly reduced carotid-femoral PWV when compared to other antihypertensives (pooled mean change difference −0.19, 95% CI: −0.59, −0.21, P=0.36, $I^2$=0%). In contrast, ACEIs significantly reduced AI

when compared to other antihypertensives (pooled mean change difference –1.84, 95% CI: –3, –0.68, P=0.002, $I^2$= 32%, P for heterogeneity =0.11). However, this difference was only significant when compared with beta-blockers (mean change difference –1.6, 95% CI: –2.84, –0.36, P=0.01). As to the comparison of ACEIs and ARBs, ACEIs have insignificantly better effect on reducing PWV (4 trials, mean change difference –0.36, 95% CI: –0.02, 0.20, P=0.21) and AI (1 trial, mean change difference –3.00, 95% CI: –25.54, 19.54, P=0.79).

Chen *et al.* conducted the present meta-analysis to compare the impact on central PWV, peripheral PWV or AI between ARB and three other classes of anti-hypertensive medications (CCB, beta-blocker, and diuretics) (13). Ten randomized controlled trials consisting of 938 patients with essential hypertension were included, and the follow-up duration ranged from 6 weeks to 18 months. The meta-analysis showed that ARB was not superior to other anti-hypertensive medications in reducing PWV in both random-effect model (4 trials) and fixed effect models (4 trials). However, the effect of ARBs to reduce AI was superior to other antihypertensive agents (3 trials, mean difference 8.94, 95% CI: 2.18–15.71, P=0.01). The included trials did not study difference between ACEIs and ARBs.

As a result, both ACEIs and ARBs are likely to de-stiffen arteries beyond BP control. RAAS activation plays a crucial role in arterial stiffness secondary to aging and hypertension and is a potential target of treatment. Interestingly, Schiffrin *et al.* studied the morphology of resistance arteries in response to treatment of essential hypertension. In patients receiving losartan, the ratio of arterial media width to luminal diameter reduced; conversely, the ratio remained unchanged in atenolol group (14). Another evidence supporting the impact of RAAS activation on arterial stiffness is the vascular change in response to treatment of primary aldosteronism (PA), a form of secondary hypertension characterized by aldosterone excess. In PA patients, adrenalectomy not only led to normalization of BP, reduction of plasma aldosterone concentration, but also lowering peripheral (brachial-ankle) and central (heart-ankle) PWVs (7,15). The improvement of PWV were due to both BP reduction and alleviation of hyperaldosteronism. Furthermore, in patients with early-stage chronic kidney disease, dual blockade by ACEI or ARB with add-on spironolactone was shown to decrease PWV significantly (16).

In conclusion, arterial stiffness is an established independent risk factor for adverse cardiac events and should be included as a part of risk assessment in patients with essential hypertension (17). Although further studies are required to investigate whether improvement PWV and AI will translate to hard outcomes, renin-angiotensin-aldosterone blockade are likely to improve arterial stiffness independent of their BP-lowering effects.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Comment on:* Chen X, Huang B, Liu M, *et al.* Effects of different types of antihypertensive agents on arterial stiffness: a systematic review and meta-analysis of randomized controlled trials. J Thorac Dis 2015;7:2339-47.

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