

## Allopurinol and arterial stiffness-what do we know so far?

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### Introduction

Allopurinol is a familiar drug that has received more attention after its antioxidant property was demonstrated across different patient's populations. This property was shown via its ability to reduce the concentration of oxidative stress markers: the frequently reported malondialdehyde, and oxidized LDL. Its ability to improve endothelial function was the subject of many small clinical trials. The promising results were expected because of the well-understood interaction between oxidative stress and endothelial dysfunction.

Arterial stiffness on the other hand is another phenomenon that is determined by smooth muscle tone influenced by vasoactive substances released from the endothelium, distending arterial pressure and vessel wall structure. Accordingly, endothelial function is an important contributor to arterial stiffness, and the ability of allopurinol to improve parameters of arterial stiffness is the natural extension from our current knowledge. Pulse wave velocity (PWV) is the 'gold standard' measure of arterial stiffness. Aortic-PWV (Ao-PWV) in particular (measured from two points: carotid and femoral) has been found to be an independent predictor of cardiovascular (CV) risk since 1999 [1]. In 2014, an individual data meta-analysis on 17,635 subjects showed that CV events increased by 30% per 1-SD increase from Aortic-PWV (95% CI 1.18-1.43) after adjustment for traditional risk factors [2]. Augmentation index is a measure of wave reflection that is considered a more recent index of arterial stiffness with less predictive value than Ao-PWV.

McEniery et al. [3] investigated the effect of aging on arterial stiffness and concluded that Ao-PWV and augmentation index change with age in non-linear pattern, with Ao-PWV being a more sensitive marker for arterial aging in individuals after the age of 50 years, while augmentation indexed being a more sensitive marker for individuals before that age. Brachial PWV (measured from two different points: carotid and radial) does change with age but less strongly than Ao-PWV. This finding is probably due to the elastic property of the aorta with elastin fatigue fracture along with media calcification with age. On the other hand, brachial artery has a higher proportion of smooth muscles and can be classified as a muscular artery.

Looking into the literature, one could find well-designed clinical trials that assess the effect of allopurinol on endothelial function and arterial stiffness simultaneously [4-8]. However, the investigators used the brachial PWV as an index of arterial stiffness, which has not shown any benefit with allopurinol therapy, despite an improvement in endothelial function in 3 of these studies [4,5,7]. Considering the well-established prognostic value of Ao-PWV and the differential remodeling between the aorta and the brachial artery, those investigators

might have achieved different results if Ao-PWV had been measured instead.

In summary, allopurinol is a promising antioxidant drug that has shown benefits of improving endothelial function on a small scale. It might have potential benefits on arterial stiffness as well, if the gold standard measure of arterial stiffness (Ao-PWV) is instead used as a method of assessment.

### References

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