Citation for published version (APA):
Reducing arterial stiffness independently of blood pressure? The randomized, factorial ‘VaSera’ trial in people with or at risk of Type 2 Diabetes

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Relationship with industry and financial disclosure: This work was funded by Fukuda Denshi, Tokyo, Japan. AJW is a share holder of HeartBeet Ltd, Suffolk, UK who manufactured and supplied the beetroot juice. CEM, VG, LF, MLC, SVM and JKC have nothing to disclose.

Brief title: Spironolactone and nitrate for arterial stiffness

Word count of manuscript: 799; number of tables: 1

Clinical Trial registration: ISRCTN25003627/ DOI 10.1186/ISRCTN25003627

Acknowledgements:
The authors thank the research nurses at Clinical Research Facility at St Thomas’ Hospital for their assistance in running the study and the patients who participated in the study. We also thank Karen McNeill for training and supervising the chemiluminescence analysis of the plasma and juices and for managing the blinding and randomization of the interventions. Finally, we thank Suzanne Barrett who worked as research administrator for all her help in ensuring the smooth running of the trial.

Key words: arterial stiffness, blood pressure, cardio-ankle vascular index (CAVI), spironolactone, dietary nitrate, beetroot, doxazosin, pulse wave velocity
**Abbreviations**

BP; blood pressure

PWV; pulse wave velocity

CAVI; cardio-ankle vascular index

T2DM; type-2 diabetes mellitus
Excess cardiac and vascular disease ‘complicates’ Type-2 diabetes (T2DM) before diagnosis. Aortic pulse wave velocity (PWV) powerfully predicts mortality in those with and at risk of T2DM independent of blood pressure (BP) (1). We tested the hypothesis that spironolactone, dietary nitrate or both could reduce PWV as a treatment target formally independent of BP in a 6-month, double-blind, parallel, randomized controlled (RCT), 2x2 factorial trial. Participants with or at risk of T2DM (n=126, 57±12 years) were randomized to spironolactone (12.5mg titrated to 25mg, twice daily) or doxazosin (4-8mg, twice daily) and dietary nitrate as ‘Beet-it’ beetroot juice (7.5mmol nitrate increased to 11.2mmol) or nitrate-free ‘Beet-it’ juice, a specific placebo (2). Outcomes were primarily change in arterial stiffness as cardio-ankle vascular index (CAVI), a nominally BP-independent measure, secondarily aortic PWV by Arteriograph, with other haemodynamic parameters measured. Outcomes were adjusted for peripheral BP differences at baseline and BP change between trial arms from the trial’s start to end, analyzed by modified ‘intention-to-treat’. CAVI₀, a measure arguably more reliably BP independent, was also calculated (3). Data are least-square means from mixed effects models adjusted as pre-specified. No statistical interactions occurred between the ‘juice’ and ‘drug’ arms.

Spironolactone and doxazosin reduced systolic BP similarly (mean[95% CI]: -7.0[-9.9,-4.2] vs. -6.3[-9.1,-3.5]mmHg, p=0.7). Reductions were borderline in CAVI and significant for aortic PWV towards doxazosin not spironolactone, contrary to our hypothesis; CAVI₀ data yielded a non-significant difference (Table 1).

The change in systolic BP was no different in the active versus placebo beetroot juice (-6.4[-9.2,-3.6] vs. -6.9[-9.8,-4.0]mmHg respectively, p=0.8). There were also no differences in change in CAVI (p=0.98) nor aortic PWV p=0.8 (Table 1). However, the difference in change in central systolic BP between active and placebo juices was highly significant -2.6[-
4.5, -0.75] mmHg, \( p = 0.007 \); differences in change of central and brachial augmentation index, other indices of arterial function that are prognostic, were borderline.

### Table 1. Difference in change from baseline for CAVI and aortic PWV between treatments

<table>
<thead>
<tr>
<th></th>
<th>CAVI</th>
<th>CAVI(_0)</th>
<th>Aortic PWV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spironolactone vs. doxazosin</td>
<td>0.25(-0.03, 0.53)</td>
<td>0.28(-0.30, 0.87)</td>
<td>0.37(0.01, 0.73)</td>
</tr>
<tr>
<td>P</td>
<td>0.080</td>
<td>0.34</td>
<td>0.045</td>
</tr>
<tr>
<td>Beetroot juice vs. placebo juice</td>
<td>0.0(-0.28, 0.29)</td>
<td>1.03(0.98, 1.08)</td>
<td>0.05(-0.31, 0.41)</td>
</tr>
<tr>
<td>P</td>
<td>0.98</td>
<td>0.38</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Data are mean(95% confidence intervals).

CAVI, cardio-ankle vascular index; CAVI\(_0\), cardio-ankle vascular index adjusted for BP (3); PWV, pulse wave velocity

*Adjusted for baseline and difference in systolic blood pressure (BP) change between the arms analyzed. Aortic PWV were also adjusted for change in systolic BP. Least square mean data were averaged over follow-up visits (3 and 6 months).

This trial suggests a proof of concept that arterial stiffness, an independent predictor of mortality generally and in T2DM (1), can be altered independently of BP, as measured by CAVI and particularly aortic PWV, if rather borderline and not as hypothesized. Clearly, detecting such change in direction of both PWV and CAVI would be underpowered. Cardiac function may have become impaired on doxazosin, as found in the ALLHAT trial, specifically in people with T2DM. Our results contrast with previous work in the Journal, in patients with mild kidney impairment, which suggested spironolactone at 25mg reduced
PWV by 0.8m/s, but that was compared against placebo (4), whereas active BP-lowering was intentionally controlled for using the interventions in this study. Despite no changes in CAVI, aortic PWV or peripheral BP in the nitrate arm, plasma [nitrate] and [nitrite] increased 4-fold and 2-fold respectively, suggesting the nitrate-nitrite-nitric oxide pathway was not interrupted. The simultaneous selective decrease in central BP on nitrate-containing juice is entirely consistent with our previous findings of normoxia-dependent conduit artery dilatation after inorganic nitrite, selectively reducing central BP (5). In conclusion, these data show the potential of reducing arterial stiffening while controlling for BP change, although adds to the debate regarding the independence of CAVI from BP. Other shorter-term evidence is available that people with diabetes do not respond to inorganic nitrate with brachial BP-lowering, nor here with change in PWV either; however, central BP is responsive. The search remains for therapeutic agents that reduce PWV safely and effectively, combined with reducing BP.

References


