

## Inter-arm blood pressure difference: more than an epiphenomenon

Invited editorial accompanying NDT-01907-2014 - Interarm systolic blood pressure as a predictor of cardiovascular events in patients with chronic kidney disease, Quiroga et al

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Differences in blood pressure measurements between arms are common; typically a systolic difference  $\geq 10$ mmHg is detected in 4.4% of subjects in unselected cohorts free of vascular disease, but prevalence rises to 7.0% in diabetes and 13.6% in the presence of hypertension.<sup>1</sup> Current hypertension guidelines therefore advocate checking both arms, and using the higher reading arm for therapeutic decisions.<sup>2</sup>

Inter-arm differences are associated with increased cardiovascular and all-cause mortality.<sup>3</sup> This association is observed in cohorts without pre-existing cardiovascular disease,<sup>4-7</sup> and also in selected cohorts with hypertension, diabetes, or established cerebrovascular disease.<sup>8-10</sup> Further cross sectional studies have demonstrated associations of systolic inter-arm differences with peripheral arterial disease,<sup>11-15</sup> increased carotid intima-media thickness,<sup>12</sup> higher coronary artery calcium scores,<sup>12</sup> and presence of left ventricular hypertrophy.<sup>11</sup> These findings have led to the recognition of inter-arm blood pressure difference as a potential risk marker for cardiovascular disease.

Chronic kidney disease is also a recognised cardiovascular risk marker.<sup>16</sup> In the context of diabetes inter-arm blood pressure differences have been associated with the presence of chronic kidney disease and albuminuria.<sup>8;17</sup> Evidence for the association of inter-arm disease and prognosis in chronic kidney disease is limited to one previous cohort study of subjects pooled from general medical and renal clinics, which found incremental increases in all-cause mortality for each 10mmHg increase in systolic inter-arm difference, with a strong additional mortality risk conferred by chronic kidney disease at any level of inter-arm difference.<sup>18</sup> The linked study of Quiroga et al [REF] in this issue provides a new insight into this relationship. They present data from 652 hypertensive subjects with relatively early (stage 1 to 3) CKD followed up for a mean of 19 months. Inter-arm difference was measured more accurately by using the mean of the second and third pairs of readings from two simultaneously activated automated sphygmomanometers. Based on these readings the authors reported high prevalences of 28% and 15% for systolic inter-arm differences  $\geq 10$ mmHg and  $\geq 15$ mmHg respectively. After adjusting for age, gender, history of cardiovascular disease, diastolic

blood pressure and use of antihypertensive medication, the authors found that inter-arm differences  $\geq 10$ mmHg and  $\geq 15$ mmHg conferred similar excess risks of 80% and 86% respectively for cardiovascular events. These findings provide the first prospective evidence for increased cardiovascular events in renal disease associated with simultaneously measured inter-arm blood pressure difference. There are, however, questions left to answer:

Simultaneous measurement methods, as used in this study, are preferred in epidemiological study as they avoid overestimation of inter-arm difference, which may in part be due to white coat effects, as well as short-term blood pressure variability.<sup>19;20</sup> However the reported prevalences of inter-arm difference in this study exceed most published estimates, only being matched by selected cohorts from vascular disease clinics.<sup>21;22</sup> Perhaps inter-arm differences are especially common in chronic kidney disease, but no trend for increasing inter-arm differences with severity of renal disease was observed, so further data to confirm these apparently high prevalences from simultaneous assessments are needed.

Survival differences were demonstrated over a short period of follow up. This has been observed in other cohorts at high baseline vascular risk,<sup>8;10;23</sup> comparison of other published hazard ratios (HR) for the combined end point of fatal and non-fatal cardiovascular events shows the current study to be within the confidence intervals of other cohorts at elevated vascular risk (pooled HR for systolic inter-arm difference  $\geq 10$ mmHg 2.7 (1.7 to 4.3)) which are higher than for unselected community cohorts at background vascular risk (HR 1.4 (1.2 to 1.7);  $p < 0.01$  for difference; figure).

Hazard ratios in this study were similar for both the  $\geq 10$ mmHg and  $\geq 15$ mmHg systolic inter-arm difference cut-off values. This lack of a “dose response” relationship has previously been observed in some,<sup>6;9;24</sup> but not in other,<sup>5;7;10</sup> cohorts reporting both cut-off values and provides a challenge to clearly delineating the independent contribution of inter-arm difference to vascular risk.

Absolute systolic blood pressure is usually found to correlate with magnitude of inter-arm difference<sup>5;25</sup> and was higher in the presence of inter-arm difference in the current study, yet the multivariate model, unusually, employed diastolic blood pressure since systolic blood pressure was not associated on univariate analysis with survival. Use of antihypertensive medications, which was adjusted for instead, may exhibit co-linearity with systolic blood pressure and be a plausible alternative variable;<sup>5</sup> smoking is another important risk factor that was not accounted for in this study. Diastolic blood pressure was negatively correlated with survival whilst systolic blood pressure was non-significantly positively correlated. This suggests that rising pulse pressure would correlate with the survival model as well, and this may offer a clue as to the aetiology of the observed inter-arm differences.

There is an assumption that inter-arm difference is due to atherosclerotic stenotic lesions,<sup>26</sup> however these have only been directly radiologically observed in large (>35mmHg) inter-arm differences.<sup>3</sup> Imaging evidence at lower levels of inter-arm difference such as 10 or 15mmHg is scarce and inconclusive.<sup>27</sup> Inter-arm differences are associated both with wider pulse pressures<sup>28</sup> and with increased pulse-wave velocities<sup>28;29</sup> Thus indirect evidence exists to suggest that arterial stiffening has a role in the aetiology of inter-arm difference.<sup>30</sup> Patients with severe CKD develop arterial calcification, which may lead to stiffened arteries, and in this case non-invasive blood pressure measurement can overestimate actual blood pressure, which if asymmetrical could also contribute to observed blood pressure differences between arms. This calcification phenomenon is not related to atherosclerosis, so this may explain the absence of significant difference in the prevalence of cardiovascular disease observed between those with and without an inter-arm difference in this study.

The uncertainties raised by this study emphasise that we do not yet have a full explanation for the cause of an inter-arm difference, or why this difference indicates an independent prognostic risk,

particularly in advanced vascular disease where it is likely to be multifactorial. There is a clear need for further mechanistic investigations to elucidate the cause.

In the case of established kidney disease, it is likely that all preventative treatment is already being prescribed. Consequently the observation of an inter-arm difference can be interpreted, in the light of this and previous studies, as a risk marker for increased cardiovascular risk, but at present this does not translate into any indication for different or more aggressive risk factor management. To date we are not aware of any evidence for offering interventions based on the detection of an inter-arm difference. We consider that a full evaluation of the role of inter-arm difference as a risk marker, and clear direct evidence to explain its pathological basis, are essential pre-requisites to any future intervention study.

#### **Conflict of Interest**

The authors declare that they have no conflicts of interest. The results presented in this paper have not been published previously in whole or part.

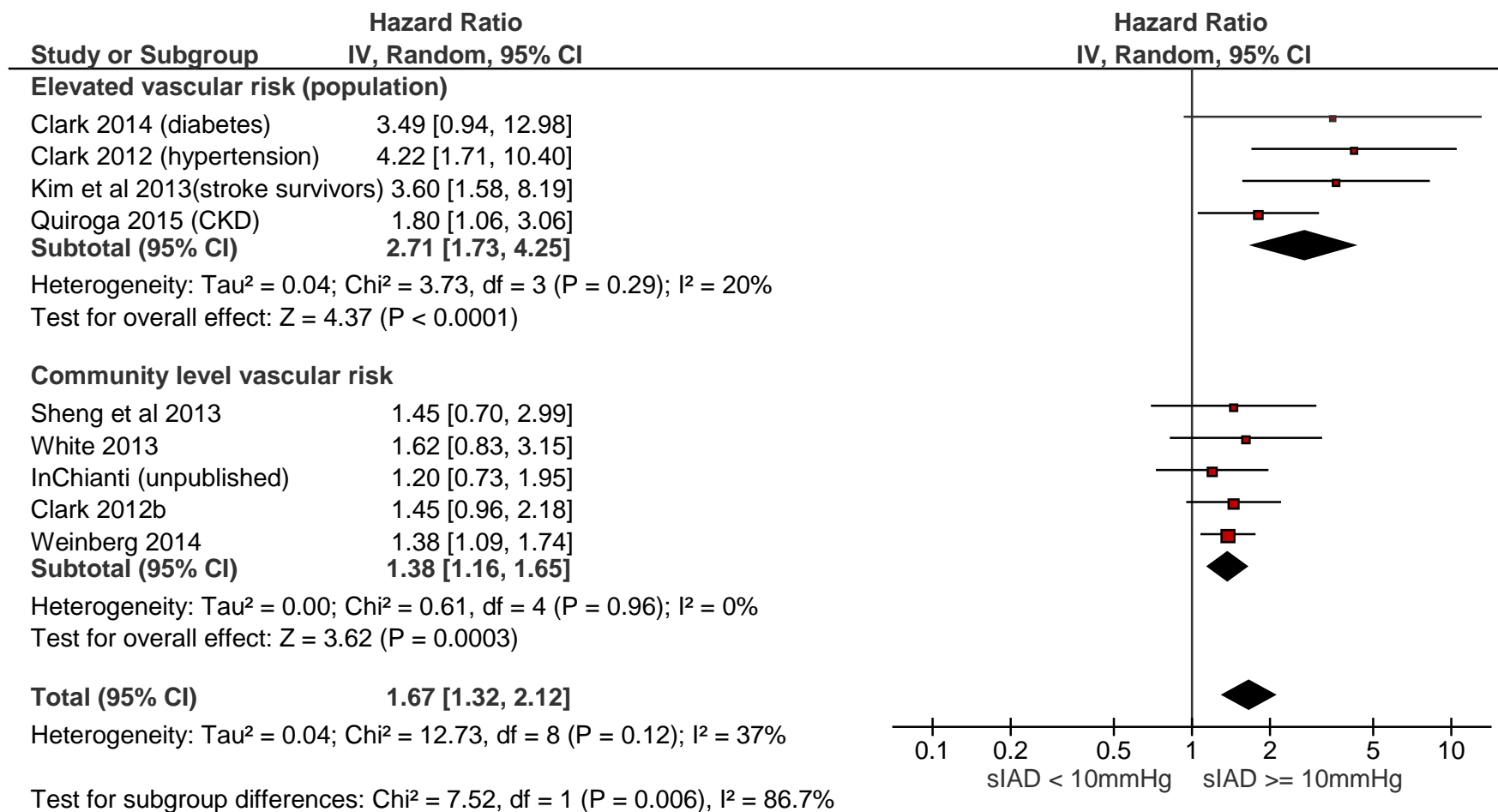
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**Figure: Meta-analysis of fully adjusted hazard ratios of a systolic inter-arm difference ≥10mmHg for fatal and non-fatal cardiovascular events stratified by underlying level of vascular risk**

sIAD = systolic inter-arm difference