Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis

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Aims
To calculate robust quantitative estimates on the predictive value of central pressures and derived central haemodynamic indices for cardiovascular (CV) outcomes and all-cause mortality by meta-analysis of longitudinal studies.

Methods and results
We meta-analysed 11 longitudinal studies that had employed measures of central haemodynamics and had followed 5648 subjects for a mean follow-up of 45 months. The age- and risk-factor-adjusted pooled relative risk (RR) of total CV events was 1.088 (95% CI 1.040–1.139) for a 10 mmHg increase of central systolic pressure, 1.137 (95% CI 1.063–1.215) for a 10 mmHg increase of central pulse pressure (PP), and 1.318 (95% CI 1.093–1.588) for a 10% absolute increase of central augmentation index (AIx). Furthermore, we found that a 10% increase of central AIx was associated with a RR of 1.384 (95% CI 1.192–1.606) for all-cause mortality. When compared with brachial PP, central PP was associated with marginally but not significantly higher RR of clinical events ($P = 0.057$).

Conclusion
Central haemodynamic indexes are independent predictors of future CV events and all-cause mortality. Augmentation index predicts clinical events independently of peripheral pressures, while central PP has a marginally but not significantly ($P = 0.057$) better predictive ability when compared with peripheral PP.

Keywords
Arterial stiffness • Augmentation index • Cardiovascular risk • Central pressure • Hypertension • Meta-analysis • Prediction • Wave reflections

Introduction
Central pressures do not correspond to brachial pressures due to pressure pulse amplification of a varying degree when moving from the aorta to the periphery. Central (aortic, carotid) pressures are pathophysiologically more relevant than peripheral pressures for the pathogenesis of cardiovascular (CV) disease.1–5 Central haemodynamics can now be reliably assessed non-invasively with a number of relatively inexpensive devices. Furthermore, despite similar effects on brachial pressure, antihypertensive drugs have differential effects on central pressure and this may explain the superiority of vasodilating drugs in recent outcome trials. However, it is mandatory for a surrogate (type 2) marker to correlate with the presence of CV disease and intermediate endpoints, and, most importantly, to predict future events. While several studies have shown an ability of central pressures and indices to predict future events, findings have not always been consistent.6–17

The present systematic review and meta-analysis was undertaken with the aim (i) to provide an overview of relevant studies, (ii) to provide an overall quantitative estimate of predictive ability of central pressures and derived indices for CV outcomes and all-cause mortality, and (iii) to test whether central indices have a better predictive ability over peripheral pressures.

Methods

Outcomes
The outcomes of interest were: (i) total CV events (CV death and nonfatal CV events—myocardial infarction, stroke, coronary artery
restenosis after percutaneous coronary intervention, revascularization, aortic syndromes); and (ii) total (all-cause) mortality.

**Study eligibility**

Studies were deemed eligible if they: (i) were full-length publications in peer-reviewed journals; (ii) evaluated one or more of the following indexes of central haemodynamics: central systolic blood pressure (SBP), central pulse pressure (PP), and central augmentation index (AIx); (iii) were longitudinal studies and reported a combined CV outcome or CV mortality or total mortality. Studies were excluded from the meta-analysis if they provided risk estimates from populations that were shared with other publications already included in the meta-analysis. No exclusion criteria were imposed with regard to the type of the population studied (healthy subjects, general population, or populations with risk factors or disease), the size of the population, or the duration of follow-up. All longitudinal studies included in the meta-analysis were prospective studies.

**Literature search**

Studies evaluating relationships of central haemodynamic indexes with the risk of future clinical events were drawn from a systematic review of the English literature in PubMed and Cochrane database up until October 2009. Key words for the search were: ‘central pressures’ or ‘aortic pressure’ or ‘augmentation index’ or ‘wave reflections’ and ‘prediction’ or ‘risk’ or ‘death’ or ‘outcome’ or ‘events’. Data sources were also identified through manually searching the references of articles.

**Extraction of data**

The search of literature, selection of studies, and extraction of data were done independently by three reviewers (C.V., K.A., K.B.). Disagreements were resolved by consensus. For central pressures, we calculated relative risks (RRs) per 10 mmHg difference. For central AIx, we calculated RRs per absolute 10% difference. For central pressures, all risk estimates were adjusted for age and risk factors. For central AIx, all but one11 of the risk estimates were adjusted for peripheral pressure or presence of hypertension. When central pressures or AIx were not analysed as continuous variables,11,16 approximate RRs per 10 mmHg change or per 10% change were calculated by available risk estimates and measures of dispersion of the BP/AIx distributions. To compare the predictive ability of central and peripheral pressures for clinical events, we calculated RRs per 1 standard deviation (SD) difference.

**Quality characteristics**

We evaluated the quality of the included studies by assessing selection bias, detection bias, and attrition bias. For control of selection bias, we assessed whether each study’s risk estimates from multivariate analysis included age, CV risk factors, and previous CV disease when necessary (and heart rate and peripheral pressure in models assessing AIx) in analysis. For control of detection bias, we recorded whether the investigators who were assessing outcomes were aware of the patient’s status of central haemodynamics. Finally, for control of attrition bias, we evaluated the extent of loss to follow-up by calculating the ratio of the number of individuals lost to follow-up to the number of clinical events in the study. This ratio comprises a measure of how loss to follow-up influenced the study’s risk estimate. We considered a loss-events ratio <15% as satisfactory control of attrition bias.

**Statistical analysis**

The risk estimates of each study were reported as a hazard ratio, RR, or odds ratio. We treated hazard ratios as RRs. Adjusted risk estimates from multivariate models were used to control for possible selection bias in the original studies.

The proportion of inconsistency across studies not explained by chance was quantified with the I² statistic. Heterogeneity between subgroups was calculated with Cochran’s Q test.18 When significant heterogeneity existed among studies, the random effects model was used to obtain the pooled RR. A fixed effects model was used when heterogeneity was absent. All tests used in our analysis were two-sided. Results were considered statistically significant at P < 0.05. The RRs and CIs of comparable studies were illustrated with forest plots.

The presence of publication bias was investigated graphically by funnel plots of precision. These plots show a study’s effect size against its precision, which is the inverse of its standard error. The implications of publication bias for our results were assessed by Duval and Tweedie’s trim-and-fill method.19 This method is based on the fact that the plot is symmetric about the summary effect in the absence of bias. A plot which is asymmetric to the right suggests an absence of studies with negative risk estimates either because of publication bias or because of a true nonexistence of negative studies (absence of publication bias). The trim-and-fill method imputes these—theoretically—missing studies, adds them to the analysis, and then re-computes the summary effect size.

All analyses were performed with Comprehensive Meta Analysis Version 2 (Biostat, Englewood, NJ, USA).20

**Results**

**Qualitative summary**

Our search identified 528 potential eligible publications, which were narrowed by preliminary review to 48 potentially relevant original articles. Further, articles were excluded because of cross-sectional study design (n = 21) and report of endpoints other than CV events or death (n = 14) or for central haemodynamic indexes other than central SBP, PP, or AIx (n = 1). One study17 provided risk estimate from a population included in another study,14 and was excluded from the meta-analysis. The CAFE Study21 was excluded because of its design (intervention, randomized trial assessing two different combinations of antihypertensive medications), and because recruitment into the CAFE study began 1 year after randomization in the ASCOT trial and thus, measurements of central haemodynamics at baseline are lacking. Finally, 11 original articles assessing relationships of central SBP, PP, or AIx with CV events and all-cause mortality were deemed eligible for our meta-analysis6–16 (Table 1).

In total, the included studies analysed 5648 subjects. Several populations such as patients with hypertension, end-stage renal disease, coronary artery disease, and subjects from general population are included. Details of the individual studies are shown in Table 1. All studies were published since 2001 and the mean/median follow-up ranged from 3 months9 to 94 months.12 Sample sizes ranged from 87 individuals6 to 2403 individuals.14

Age, gender, other risk factors for CV disease, and previous CV disease when necessary were controlled for in most of the studies (Table 1). Most studies assessing AIx adjusted for heart rate. Only a few studies report explicitly that outcomes were assessed in a blind manner.7,14 The loss-events ratio ranged from 0.7 to 15%.13 and it was less than 15% in all studies reporting number of patients lost to follow-up (Table 1).
### Table 1: Overview of studies on the association between central pressures and augmentation index and clinical endpoints sorted by date of publication

<table>
<thead>
<tr>
<th>Study</th>
<th>Population-sample size</th>
<th>Age (year)</th>
<th>Men (%)</th>
<th>Follow-up duration</th>
<th>Events</th>
<th>Index</th>
<th>Modality</th>
<th>Attrition bias (loss/events ratio)</th>
<th>Index modelled in</th>
<th>Adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu et al.⁶</td>
<td>Stable CAD/angioplasty (n = 87)</td>
<td>72.5 ± 5.1</td>
<td>92</td>
<td>6.1 ± 4.1 m</td>
<td>39 cases of restenosis</td>
<td>Aortic PP, aortic PPF, aortic PI</td>
<td>Invasive (fluid-filled system, 7F pig-tail catheter)</td>
<td>Not reported</td>
<td>Continuous; optimal cut-off by ROC curve</td>
<td>Risk factors for restenosis (not specified)</td>
</tr>
<tr>
<td>London et al.⁷</td>
<td>ESRD (n = 180)</td>
<td>54 ± 16</td>
<td>60</td>
<td>52 ± 36 m</td>
<td>70 deaths; 40 CV deaths</td>
<td>Carotid Alx</td>
<td>Tonometry of CCA</td>
<td>0%</td>
<td>Continuous; quartiles; optimal cut-off by ROC curve</td>
<td>Age, sex, diastolic BP, HR, smoking, duration of dialysis, blood chemistry analyses, ACE-inhibitor prescription, PWV</td>
</tr>
<tr>
<td>Safar et al.⁸</td>
<td>ESRD (n = 180)</td>
<td>54 ± 16</td>
<td>60</td>
<td>52 ± 36 m</td>
<td>70 deaths; 40 CV deaths</td>
<td>Carotid SBP, PP, brachial-carotid PP amplification</td>
<td>Tonometry of CCA</td>
<td>0%</td>
<td>Continuous; tertiles</td>
<td>Age, time on dialysis, previous CV events</td>
</tr>
<tr>
<td>Ueda et al.⁹</td>
<td>CAD/angioplasty (n = 103)</td>
<td>62 ± 9</td>
<td>78</td>
<td>6 m</td>
<td>36 cases of restenosis</td>
<td>Aortic Alx; aortic inflection time</td>
<td>Invasive (fluid-filled system, 5F pig-tail catheter)</td>
<td>0%</td>
<td>Continuous; tertiles</td>
<td>Age, sex, smoking, hypertension, diabetes, hypercholesterolaemia, stent size, HR, inflection time</td>
</tr>
<tr>
<td>Chirinos et al.¹⁰</td>
<td>CAD or non-obstructive coronary atherosclerosis (n = 297)</td>
<td>63.8 ± 10.3</td>
<td>100</td>
<td>40 ± 14 m</td>
<td>58 deaths; 128 CV events</td>
<td>Aortic PP, AP, Alx</td>
<td>Invasive (low-compliance fluid filled system)</td>
<td>11%</td>
<td>Continuous</td>
<td>Age, diastolic or mean BP, diabetes, smoking, HR, height, use of drugs, lipid levels, ejection fraction, CRP, extent of CAD</td>
</tr>
<tr>
<td>Weber et al.¹¹</td>
<td>CAD/angioplasty (n = 262)</td>
<td>65 ± 10</td>
<td>71</td>
<td>24 m</td>
<td>12 deaths; 61 CV events</td>
<td>HR-corrected aortic Alx</td>
<td>Tonometry of RA—transfer function</td>
<td>1.6%</td>
<td>Continuous; tertiles</td>
<td>Age, sex, smoking, preeclampsia, diabetes, peripheral artery disease, extent of CAD, medications, triglycerides, creatinine clearance, BMI, SBP, or PP</td>
</tr>
<tr>
<td>Dart et al.¹²</td>
<td>Elderly female hypertensives (n = 484)</td>
<td>72 ± 5</td>
<td>0</td>
<td>49 m (median)</td>
<td>53 CV events</td>
<td>Carotid SBP, PP, Alx</td>
<td>Tonometry of CCA</td>
<td>Not reported</td>
<td>Dichotomous</td>
<td>Age, cholesterol, smoking</td>
</tr>
<tr>
<td>Covic et al.¹³</td>
<td>ESRD (n = 92)</td>
<td>42.6 ± 11.2</td>
<td>54</td>
<td>61 ± 25 m</td>
<td>15 deaths</td>
<td>HR-corrected aortic Alx</td>
<td>Tonometry of RA—transfer function</td>
<td>Not reported</td>
<td>Tertiles</td>
<td>Age, sex, time on dialysis, SBP, BP, LVMi, use of ACE inhibitors</td>
</tr>
<tr>
<td>Roman et al.¹⁴</td>
<td>American Indians free of CVD (n = 2403)</td>
<td>63.5 ± 7.5</td>
<td>35</td>
<td>58 ± 16 m</td>
<td>386 deaths; 67 CV deaths; 319 CV events</td>
<td>Aortic SBP, PP</td>
<td>Tonometry of RA—transfer function</td>
<td>0.8%</td>
<td>Continuous</td>
<td>Age, sex, current smoking, BMI, total/HDLC ratio, creatinine, fibrinogen, diabetes, HR</td>
</tr>
<tr>
<td>Jankowski et al.¹⁵</td>
<td>Subjects undergoing non-emergency coronary angiography (n = 1109)</td>
<td>52.7 ± 19.2</td>
<td>74</td>
<td>52.7 ± 19.2 m</td>
<td>90 deaths; 71 CV deaths; 246 CV events</td>
<td>Aortic PP, PPF</td>
<td>Invasive (low-compliance fluid filled system)</td>
<td>15%</td>
<td>Continuous; quartiles</td>
<td>Age, sex, ejection fraction, mean coronary artery stenosis, heart failure, HR, risk factors, CVD, GFR, drugs</td>
</tr>
<tr>
<td>Pini et al.¹⁶</td>
<td>Community-dwelling individuals ≥ 65 year (n = 398)</td>
<td>73 ± 6</td>
<td>45</td>
<td>94 ± 24 m</td>
<td>106 deaths; 45 CV deaths; 122 CV events</td>
<td>Aortic SBP, PP, Alx</td>
<td>Tonometry of CCA</td>
<td>Not reported</td>
<td>Continuous</td>
<td>Age, sex</td>
</tr>
</tbody>
</table>

Alx, augmentation index; BMI, body-mass index; BP, blood pressure; CAD, coronary artery disease; CCA, common carotid artery; CV, cardiovascular; CVD, CV disease; DBP, diastolic blood pressure; ESRD, end-stage renal disease; HR, heart rate; LVMi, left ventricular mass index; PCI, percutaneous coronary intervention; PI, pulsatility index (PP/DBP); PP, pulse pressure; PPF, fractional pulse pressure (PP/mean BP); PWV, pulse wave velocity; RA, radial artery; SBP, systolic blood pressure.
Meta-analysis

Central systolic blood pressure
There was no significant heterogeneity among the three relevant studies (total \(n = 3285; \, i^2 = 55.1, \, P = 0.11\)). Overall, the fixed effects model showed that the RR of total CV events for an increase of central SBP by 10 mmHg was 1.088 (95% CI 1.040–1.139), corresponding to a risk increase of 8.8% (Figure 1).

Central pulse pressure
There was significant heterogeneity among the six relevant studies (total \(n = 4778; \, i^2 = 58.5, \, P = 0.034\)). Overall, the random effects model showed that the RR of total CV events for an increase of central PP by 10 mmHg was 1.137 (95% CI 1.063–1.215) corresponding to a risk increase of 13.7% (Figure 2). If the study of Lu et al.6 (which evaluates only coronary restenosis post-angioplasty) is excluded from analysis, the random effects model showed that the respective RR was 1.123 (95% CI 1.079–1.169, \(P < 0.001\)), corresponding to a risk increase of 12.3%.

Central augmentation index

Cardiovascular events
We observed significant heterogeneity among the five relevant studies (total \(n = 1326; \, i^2 = 63.3, \, P = 0.028\)). Overall, the random effects model showed that the RR of total CV events for an absolute increase of central Alx by 10% was 1.318 (95% CI 1.093–1.588), corresponding to a risk increase of 31.8% (Figure 3A). If the study of Ueda et al.8 (which evaluates only coronary restenosis post-angioplasty) is excluded from the analysis, the random effects model showed that the respective RR was 1.264 (95% CI 1.037–1.542, \(P = 0.02\)), corresponding to a risk increase of 26.4%.

Total mortality
We did not observe significant heterogeneity among the three relevant studies (total \(n = 569; \, i^2 = 42.9, \, P = 0.17\)). Overall, the fixed effects model showed that the RR of total mortality for an absolute increase of central Alx by 10% was 1.384 (95% CI 1.192–1.606), corresponding to a risk increase of 38.4% (Figure 3B).

Comparison of predictive ability between central and brachial pressures
Five studies reported relationships of risk of clinical events with both central and brachial PP. Meta-analysis of these studies revealed that both central PP and brachial PP are significantly associated with clinical events, and that central PP is associated with a marginally but not significantly higher RR of clinical events than brachial PP [1.318 (95% CI 1.221–1.423) vs. 1.236 (95% CI 1.128–1.354), \(P = 0.057\), Figure 4A]. In contrast, analysis of four studies reporting risk as a function of central and brachial SBP showed similar risk estimates for central SBP and brachial SBP [1.236 (95% CI 1.128–1.354) vs. 1.204 (95% CI 1.104–1.313), \(P = 0.62\), Figure 4B].
The present study is the first meta-analysis to provide documents supporting the predictive role of central haemodynamics and indices in clinical events for a 1 standard deviation increase in pulse pressure and systolic pressure, according to the site of measurement (central vs. brachial). Boxes represent the RRs and lines represent the 95% CI for individual studies. The diamonds and their width represent the pooled RR and the 95% CI, respectively.

### Publication bias

The funnel plots for the relationships of central SBP, PP, and Alx with total CV events and for the relationship of central Alx with total mortality were not symmetric (Figure 5). The trim-and-fill method imputed missing studies and recalculated our pooled risk estimate. The imputed RRs were not substantially different from the initial estimates, suggesting the absence of significant publication bias.

### Discussion

In this systematic review and meta-analysis, we pooled data of 5648 subjects from available published studies who were followed up for a mean of 45 months. Our analysis indicates that central pressures and indices confer a significant predictive value of CV events (all indices) and all-cause mortality (Alx only) in a range of populations. The predictive value of central Alx is independent of blood pressure and heart rate, while central PP has a marginally but not significantly better predictive ability compared with brachial PP. These findings add to the mounting evidence that central PP has a marginally but not significantly better predictive value compared with peripheral PP and that Alx has a predictive value independent of peripheral pressures, further evidence is needed. The degree of pressure amplification towards the periphery is variable, depending on a number of factors including age, gender, and heart rate. Accordingly, extension of the existing data regarding the predictive ability of central haemodynamic indexes over and above brachial BP in a wider range of populations and disease states is mandatory and results should be corrected for potential confounders. Future studies aiming at comparison between central and peripheral pressures should report predictive values on both central and peripheral pressures. Data on detection and attrition bias must be reported in original studies and every effort should be made to reduce these sources of bias in order to avoid overestimation of risk. Furthermore, it should be noted that evidence for a specific central pressure component or index does not necessarily apply to the others. Central pressures may be more easily adopted by the clinician compared with calculated indices, such as Alx and amplification, but, on the other hand, they may be more prone to error since they rely on the (in)accuracy of the cuff measurement. For a better understanding of the predictive value of newly introduced indices, such as Alx, clinicians should be familiarized with the magnitude of their changes over a range of conditions (e.g. with ageing,29,30 with drug treatment22–25 and with physiological variations, such as diurnal variation,32 variation with menstrual cycle,32 changes with exercise,33 etc.). Ideally, in studies aiming at comparison between central and peripheral pressures, information study overcomes the potentially biased inclusion and weighing of results that may appear in narrative reviews. Furthermore, we dealt with potential publication bias. Although there are some limitations in the evaluation of publication bias when few studies are considered, our analysis indicates that any publication bias may have accounted only for a slight overestimation of a true predictive role of central haemodynamic indexes for clinical outcomes. Taking into consideration first, the differential effect of antihypertensive drugs on central BP,21–26 and, second, the predictive value of central BP for CV events, it can be explained, at least partly, why drugs with similar reduction in peripheral pressures have a differential impact on surrogate endpoints (such as left ventricular mass27) and CV events.27

The predictive value of central haemodynamics is based on their pathophysiological importance. It is aortic systolic pressure that the left ventricle encounters during systole (afterload) and the aortic pressure during diastole is a determinant of coronary perfusion. Furthermore, the distending pressure in the large elastic-type arteries (aorta and carotid) is a key determinant of the degenerative changes that characterize accelerated ageing and hypertension. In contrast, the muscular peripheral arteries such as the brachial and the radial ones are less influenced by these changes.1–5

Arterial stiffness is being adopted in clinical practice,2,3,27,28 and our findings offer support to the clinical implementation of central haemodynamics as well: clinicians should be familiarized with terms such as central pressures and haemodynamics, and such parameters could be included in the evaluation of the patient if feasible. However, several issues should be further resolved. Although our findings show that central PP has a marginally but not significantly better predictive value compared with peripheral PP and that Alx has a predictive value independent of peripheral pressures, further evidence is needed. The degree of pressure amplification towards the periphery is variable, depending on a number of factors including age, gender, and heart rate. Accordingly, expansion of the existing data regarding the predictive ability of central haemodynamic indexes over and above brachial BP in a wider range of populations and disease states is mandatory and results should be corrected for potential confounders. Future studies aiming at comparison between central and peripheral pressures should report predictive values on both central and peripheral pressures. Data on detection and attrition bias must be reported in original studies and every effort should be made to reduce these sources of bias in order to avoid overestimation of risk. Furthermore, it should be noted that evidence for a specific central pressure component or index does not necessarily apply to the others. Central pressures may be more easily adopted by the clinician compared with calculated indices, such as Alx and amplification, but, on the other hand, they may be more prone to error since they rely on the (in)accuracy of the cuff measurement. For a better understanding of the predictive value of newly introduced indices, such as Alx, clinicians should be familiarized with the magnitude of their changes over a range of conditions (e.g. with ageing,29,30 with drug treatment22–25 and with physiological variations, such as diurnal variation,32 variation with menstrual cycle,32 changes with exercise,33 etc.). Ideally, in studies aiming at comparison between central and peripheral pressures, information...
for a wide range of central pressure components and indices (namely carotid and aortic SBP and PP, second systolic pressure peak of the peripheral pressure waveform, Alx, amplification) should be reported. Furthermore, it is crucial to determine the shape (e.g. linear) of the relationship between central haemodynamic indices and risk. Important ongoing studies, such as the Anglo-Cardiff Collaborative Trial, Asklepios, ENIGMA, European Network for Non-invasive Determination of Large Arteries, National Institute of Aging, Framingham, and Proteger, are anticipated to shed light on these issues. Until then, it cannot be overemphasized that brachial BP remains the point of reference for the management of the hypertensive patient.

We acknowledge the limitation that in this analysis we used aggregate data as reported or calculated in published articles, rather than data of individual patients. Accordingly, we have not dealt with potential methodological problems of the original studies. Although we showed that the predictive role of Alx is independent of peripheral pressures, its ability to discriminate, calibrate, and reclassify risk could not be strictly assessed, as most of the studies we included do not provide such data. Aortic and carotid pressures (either SBP or PP) were analysed as a group and this may have affected the exact RRs found. Due to the small number of relevant studies in the literature, our study is not powered to explain possible heterogeneity between original studies and to calculate robust estimates, so further original studies are needed.

In conclusion, central pressure components and indices predict independently future clinical events. Specifically for central PP, this ability is marginally but not significantly better compared with peripheral pressures, while Alx predicts clinical events independently of peripheral pressures. Superiority of vasodilating drugs regarding outcome may be partly due to their differential effects on central pressure despite similar effects on brachial pressure. Central haemodynamics show the potential to be implemented in clinical practice. Future studies should provide data on a wider range of populations and disease states and they should elaborate on the ability of central indexes to discriminate, calibrate, and reclassify the risk of patients.

Conflict of interest: M.F.O. is a founding director of AtCor Medical Pty Limited, manufacturer of systems for analysing the arterial pulse.

References


