Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a meta-analysis of longitudinal studies

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Disclosures

No conflict of interest
Expert consensus document on arterial stiffness: methodological issues and clinical applications

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Box 2: Position statement: PWV. Carotid-femoral PWV is considered as the ‘gold-standard’ measurement of arterial stiffness.
Arterial stiffness and risk stratification

Increased pulse wave velocity is added to the list of factors influencing prognosis as an early index of hypertension-related target organ (large artery) damage.
Arterial elastic properties

- There is a general impression that arterial stiffness has a significant predictive role based on the results of individual studies.

- Several narrative reviews supporting the predictive role of arterial stiffness have been published to date
  
  Zieman SJ, Melenovsky V, Kass DA. ATVB 2005
  Vlachopoulos C, Aznaouridis K, Stefanadis C. Heart 2006
  McEniery C, Cockcroft JR. Adv Cardiol 2007
  Kullo IJ, Malik AR. JACC 2007

- However, no overall quantitative estimate of this role exists.
Purposes of meta-analysis

- To calculate quantitative estimates of the predictive value of aortic PWV for outcomes (total CV events, CV mortality, all-cause mortality)

- To evaluate whether aortic PWV portends a different predictive ability in populations with different estimated baseline CV risk.

- To investigate whether publication bias could have affected the estimated predictive ability of aortic PWV
Outcomes of meta-analysis

1) total CV events
2) CV mortality
3) total (all-cause) mortality

Study eligibility

1) full-length publications in peer-reviewed journals
2) evaluated aortic PWV
3) reported a combined CV outcome or CV mortality or total mortality
Literature search


- The search terms were “stiffness,” “arterial stiffness,” “arterial elasticity,” or “pulse wave velocity,” and “prediction,” “risk,” “death,” “mortality,” “outcome,” or “events.”
Data & Statistics

- Aggregate data reported in published articles were used for analysis (no data of individual patients).

- The risk estimates of each study were reported as a hazard ratio, relative risk (RR) or odds ratio.

- The predictive ability of aortic PWV was evaluated for:
  - high (vs low) aortic PWV
  - increase of 1 SD
  - increase of 1 m/sec

- Patients were allocated to high or low aortic PWV groups according to cutoffs provided by each study (median, upper tertile, optimal cutoff derived by ROC curves)

- When possible, adjusted risk estimates from multivariate models were used to control for possible selection bias in the original studies.

- A random effects model was used to obtain the pooled RR.

- All analyses were performed with Comprehensive Meta Analysis Version 2 (Biostat, Englewood, New Jersey).
Qualitative summary

Our search identified 126 publications, which were narrowed by preliminary review to 40 potentially relevant original articles.

Of those, 23 studies were excluded because of 1) cross-sectional study design (n =5), or 2) measurement of stiffness indexes other than aPWV (n =4), or 3) report of end points other than CV events or death (n =11), or had the whole population or part of the population in common (n=3).

Our meta-analysis included 17 original articles following 15,877 subjects for a mean follow-up of 7.7 years.

All studies were published since 1999.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Population-Sample size</th>
<th>Follow-up</th>
<th>Events</th>
<th>Modality</th>
<th>aPWV cut-off (high vs. low)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson 2009</td>
<td>Non-diabetic general population (N=174)</td>
<td>19.6 y</td>
<td>58 deaths</td>
<td>Doppler flow</td>
<td>upper tertile</td>
</tr>
<tr>
<td>Blacher 1999</td>
<td>ESRD (N=241)</td>
<td>6 y</td>
<td>73 deaths, 48 CV deaths</td>
<td>Doppler flow</td>
<td>upper tertile</td>
</tr>
<tr>
<td>Boutouyrie 2002</td>
<td>Hypertension (N=1,045)</td>
<td>5.7 y</td>
<td>53 coronary events, 97 CV events</td>
<td>pressure transducer (Complior)</td>
<td>upper tertile</td>
</tr>
<tr>
<td>Choi 2007</td>
<td>chest pain patients (N=497)</td>
<td>2.6 y</td>
<td>1 death, 0 CV death, 120 CV events</td>
<td>fluid-filled system (5F right Judkins catheter)</td>
<td>upper tertile</td>
</tr>
<tr>
<td>Cruickshank 2002</td>
<td>Diabetes (N=394)</td>
<td>10.7 y</td>
<td>179 deaths</td>
<td>Doppler flow</td>
<td>3.8 m/sec increase</td>
</tr>
<tr>
<td>Laurent 2001</td>
<td>Hypertension (N=1,980)</td>
<td>9.3 y</td>
<td>107 deaths, 46 CV deaths</td>
<td>Pressure transducer (Complior)</td>
<td>5 m/sec increase</td>
</tr>
<tr>
<td>Mattace-Raso 2006</td>
<td>Community based adults (N=2,835)</td>
<td>4-9 y</td>
<td>352 deaths, 156 CV events</td>
<td>pressure transducer (Complior)</td>
<td>gender-specific upper tertile</td>
</tr>
<tr>
<td>Meaume 2001</td>
<td>Subjects &gt;70 y (N=141)</td>
<td>2.5 y</td>
<td>27 CV deaths</td>
<td>pressure transducer (Complior)</td>
<td>upper decile</td>
</tr>
<tr>
<td>Mitchell 2010</td>
<td>General population (N=2,232)</td>
<td>7.8 y</td>
<td>151 CV events</td>
<td>Arterial tonometry</td>
<td>median</td>
</tr>
<tr>
<td>Pannier 2005</td>
<td>ESRD (N=305)</td>
<td>5.8 y</td>
<td>96 CV deaths</td>
<td>pressure transducer (Complior)</td>
<td>upper tertile</td>
</tr>
<tr>
<td>Shoji 2001</td>
<td>ESRD (N=265)</td>
<td>5.3 y</td>
<td>81 deaths, 36 CV deaths</td>
<td>PWV meter (PWV-200)</td>
<td>median</td>
</tr>
<tr>
<td>Shokawa 2005</td>
<td>Ethnic minority (N=492)</td>
<td>10 y</td>
<td>43 deaths, 14 CV deaths</td>
<td>pressure transducer (MCG400)</td>
<td>optimal cut-off by ROC curve</td>
</tr>
<tr>
<td>Sutton-Tyrrell 2005</td>
<td>Community-based old adults (N=2,488)</td>
<td>4.6 y</td>
<td>265 deaths, 111 CV deaths</td>
<td>Doppler flow</td>
<td>Gender-specific median</td>
</tr>
<tr>
<td>Terai 2008</td>
<td>Hypertension (N=676)</td>
<td>4.8 y</td>
<td>22 deaths, 88 CV events</td>
<td>pressure transducer (FCP-4731 device)</td>
<td>median</td>
</tr>
<tr>
<td>Wang 2010</td>
<td>General population (N=1,272)</td>
<td>15 y</td>
<td>225 deaths, 64 CV deaths</td>
<td>Doppler flow</td>
<td>2.3-3.5 m/sec increase</td>
</tr>
<tr>
<td>Willum-Hansen 2006</td>
<td>General population (N=1,678)</td>
<td>9.4 y</td>
<td>62 CV deaths, 154 CV events</td>
<td>piezoelectric pressure transducers (Hellige GmbH)</td>
<td>upper quintile</td>
</tr>
<tr>
<td>Zoungas 2007</td>
<td>ESRD (N=207)</td>
<td>3.6 y</td>
<td>17 CV deaths, 65 CV events</td>
<td>pressure transducer (Millar Mikro-tip, SPT-301)</td>
<td>&gt;9.9 m/sec (cut-off)</td>
</tr>
</tbody>
</table>
Results (tertiles)

Pooled RR of clinical events increases in a stepwise, linear-like fashion from the first to the third tertile of aortic PWV
Compared to low PWV, the pooled RR of total CV events, CV mortality and all-cause mortality for high PWV patients was 2.26, 2.02 and 1.90, respectively.
For an increase in PWV by 1 m/sec, the pooled RR of total CV events, CV mortality and all-cause mortality is 1.14, 1.15 and 1.15, respectively (the estimated risk increases by 14%, 15% and 15%).
Results (1 SD increase)

For an increase in PWV by 1 SD, the pooled RR of total CV events, CV mortality and all-cause mortality is 1.47, 1.47 and 1.42, respectively (the risk increases by 47%, 47% and 42%).
Results (high vs low risk groups)

The pooled RR of total CV events and CV death was significantly higher in high-risk populations compared with low-risk populations.

Low risk group: general population

High risk group: CAD, ESRD, HTN, DM
Results

Publication bias analysis

- Funnel plots of precision
- Trim-and-fill method (imputes theoretically missing studies and recalculates the pooled RR)
- Fail-safe N test (computes the number of theoretically missing studies with a mean effect of zero that would need to be added to the analysis to yield a statistically non-significant overall effect)

Publication bias is not sufficient to influence our findings in a meaningful way
Summary of findings

- In populations with high PWV, the risk of CV events, CV mortality and all-cause mortality is almost twice as high compared with the risk in patients with low PWV.

- For an increase in aortic PWV of 1 m/s or of 1 SD, the risk increases by more than 10% or 40%, respectively.

- The predictive value of increased aortic PWV is higher in patients with higher risk disease states.
Limitations

- Use of aggregate -summary- data (no data of individual patients).

- To define high and low aortic PWV, we used the cutoff values used by each study, because there are no established cutoffs for PWV.

- Although CV mortality and all-cause mortality were uniformly defined, the definition of total CV events differed among the studies.
Prediction of Cardiovascular Events and All-Cause Mortality With Arterial Stiffness

A Systematic Review and Meta-Analysis

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Objectives
The purpose of this study was to calculate robust quantitative estimates of the predictive value of aortic pulse wave velocity (PWV) for future cardiovascular (CV) events and all-cause mortality by meta-analyses of longitudinal studies.

Background
Arterial stiffness is increasingly recognized as a surrogate end point for CV disease.

Methods
We performed a meta-analysis of 17 longitudinal studies that evaluated aortic PWV and followed up 15,877 subjects for a mean of 7.7 years.

Results
The pooled relative risk (RR) of clinical events increased in a stepwise, linear-like fashion from the first to the third tertile of aortic PWV. The pooled RRs of total CV events, CV mortality, and all-cause mortality were 2.26 (95% confidence interval: 1.89 to 2.70, 14 studies), 2.02 (95% confidence interval: 1.68 to 2.42, 10 studies), and 1.90 (95% confidence interval: 1.61 to 2.24, 11 studies), respectively, for high versus low aortic PWV subjects. For total CV events and CV mortality, the RR was significantly higher in high baseline risk groups (coronary artery disease, renal disease, hypertension) compared with low-risk subjects (general population). An increase in aortic PWV by 1 m/s corresponded to an age-, sex, and risk factor–adjusted risk increase of 14%, 15%, and 15% in total CV events, CV mortality, and all-cause mortality, respectively. An increase in aortic PWV by 1 SD was associated with respective increases of 47%, 47%, and 42%.

Conclusions
Aortic stiffness expressed as aortic PWV is a strong predictor of future CV events and all-cause mortality. The predictive ability of arterial stiffness is higher in subjects with a higher baseline CV risk. (J Am Coll Cardiol 2010;55:1318–27) © 2010 by the American College of Cardiology Foundation
Conclusions

- Aortic stiffness expressed by aortic PWV is a strong predictor of future CV events, CV mortality and all-cause mortality.

- The predictive ability of arterial stiffness is higher in subjects with a higher baseline CV risk.
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