Pulse Wave Velocity: An independent predictor of cardiovascular death and disability

Prepared for the Swiss Re Insurance Medicine Summit 2014
A new assessment tool for improved risk stratification – Arterial Stiffness as measured by Pulse Wave Velocity (PWV)

Arterial stiffness is an independent prognostic biomarker of cardiovascular risk\(^1\) substantiated by extensive literature once it could be easily measured and quantified by Pulse Wave Velocity (PWV). Arterial Stiffness is related to PWV (as measured in m/s) because the pulse wave travels faster in a stiff artery than in a supple one.

**PWV and insurance industry**
What brings us to the insurance industry now is a recent comprehensive meta-analysis demonstrating that PWV is an independent predictor of cardiovascular (CV) events which enables for a Net Reclassification Index (NRI) of 10–20%. PWV improves the risk prediction already based on traditional factors of age, gender, systolic blood pressure, cholesterol and smoking (the standard Framingham risk factors). The change in PWV as the aorta becomes stiffer with age\(^2\) is exemplified in Figure 1. This “vascular aging” is not only dependent on chronological aging itself but is also affected by genetics, lifestyle (physical inactivity, smoking, diet etc) and disease (diabetes, hypertension, chronic kidney disease, CKD, inflammatory diseases, etc).

![Fig. 1: Age-dependent progression of pulse wave velocity (PWV) among 998 healthy subjects](#)

**Simple measurement method**
PWV is measured tonometrically or with oscillometric systems. Today, PWV and blood pressure measurement can be combined in one device, using a simple upper arm oscillometric technique. The measurement accuracy compared with invasive catheter technology has been examined and published.

“The value of Pulse Wave Velocity in risk assessment and treatment decisions has been recognized by the European Society of Cardiology and the European Society of Hypertension”\(^3\)
Clinical background:
The clinical and prognostic significance of PWV

A recent meta-analysis of 17,635 individual subjects from 16 longitudinal studies showed that PWV was a strong independent predictor of mortality and cardiac and stroke events. This was in addition to all other wellknown predictors such as hypertension and diabetes. The association was present at all ages and was strongest under 60 years of age and in the intermediate risk quartiles. PWV enhanced the prediction of 10-year risk of CV disease by an average 13% beyond all other predictors such as age, sex, blood pressure, smoking, diabetes and cholesterol, as seen in the hazard ratios in Figure 2.

Fig. 2: Hazard ratios (red) after including pulse wave velocity (PWV) (1-SD Increase in Loge-Transformed aPWV), adjusted for age, sex group, systolic blood pressure, cholesterol, HDL cholesterol, smoking status, and presence of diabetes, and anti-hypertensive medication

“PWV improves the prediction of life expectancy beyond traditional risk factors”
An increase in PWV has been shown to be associated with, and sometimes to precede conditions that themselves are strong predictors of subsequent additional morbidity, as exemplified by hypertension and diabetes preceding chronic kidney disease (CKD).

**Hypertension**
The strong association between increased PWV and hypertension, particularly in the elderly has long been known but more recently it has been shown to also precede (thus predict) hypertension in two successive exam cycles of the longitudinal Framingham Heart Study. This is probably the strongest example to date of the ability of PWV to predict an important disease that is the dominant cause of CV morbidity and mortality. While the same authoritative data for PWV as predictor of other diseases does not yet exist, the summaries below will clarify why it seems likely for diseases such as CKD, vascular dementia, and diabetes progression.

**CKD**
An increase in PWV in CKD has been shown to be a predictor of CV outcomes in CKD. In this study it was especially true if the PWV did not lower in response to the lowering of BP, in which case they had a 2.6-fold greater risk of all-cause and cardiovascular death during an average observation of 3.5 years. These data do not directly address whether PWV predicts future development or accelerated deterioration. However, such relationship of PWV to the rate of progression of renal disease in patients that already have varying stages of CKD has been shown in several studies. In one study a prediction of incident CKD by arterial stiffness proved negative in a healthy cohort with a 5–7 year observation period and a small segment with mild to moderate CKD. This is not surprising given the natural history of the disease at early stages and the short longitudinal duration of the study. Clear demonstration of prediction will require larger and longer studies. It is not unreasonable to presume that increased PWV predicts future development of CKD in patients with predisposing diseases such as diabetes and hypertension since increased PWV has been shown to be associated with several renal hemodynamic variables and many of these renal hemodynamic factors are involved in the progression to or of renal disease. As an example, PWV has been shown to predict the development of renal deterioration in contrast-induced nephropathy, a condition mediated by renal hemodynamic factors.
Vascular Dementia
Increased large artery stiffness has been shown to be associated with cognitive dysfunction in vascular dementia and Alzheimer’s disease\textsuperscript{15} and with cognitive decline in multiple cognitive domains\textsuperscript{16} in cross-sectional studies. Because cross-sectional studies can not shed light on whether arterial stiffness causes cognitive decline, a meta-analysis was conducted on the available longitudinal studies and showed, in four relevant studies, that increased PWV indeed predicted cognitive decline over an average of only 5 years of follow-up\textsuperscript{17}. Arterial stiffness increases pulsatility in the arteries perfusing the brain and this increased pulsatility has been linked to decreased cognition\textsuperscript{18} and has been shown to cause direct harm to the brain observed on imaging\textsuperscript{19}. Given the mortality, disability and cost of care associated with dementia of all forms, the implications of decreased PWV as predictor of mortality are obvious. Whether improvement in arterial stiffness, possibly achievable by lifestyle modifications, such as exercise and diet, or by drugs, such as anti-hypertensive and cholesterol lowering agents, will prevent or delay cognitive decline is not known. However, it is reassuring that exercise, which has been shown to improve arterial stiffness\textsuperscript{20,21}, has also been shown to delay cognitive decline\textsuperscript{22,23}.

Diabetes
The association of increased arterial stiffness with diabetes\textsuperscript{24} and with CV morbidity and mortality in diabetes\textsuperscript{25,26} is well known. In patients with known diabetes, a high PWV identifies those who are at higher risk of developing a fatal cardiac event or stroke. However, increased glycemia also induces glycation and cross-linking of other proteins, such as collagen and elastin in the vessel walls, and these advanced glycation end-products cause arterial stiffening\textsuperscript{27,28}. Since glycation is a continuous process based on the aggregate level of hyperglycemia over time, starting even in the pre-diabetes stage, it is intuitive that elevated PWV should precede the occurrence of overt diabetes, although, to date, there is no study analogous to the one available for hypertension\textsuperscript{5} as stated above, to demonstrate that PWV elevation preceded incident diabetes.

“The risk of cardiovascular events, particularly in people with medium risk, can be reclassified by measuring PWV. The measurement of PWV can be easily done by a blood pressure cuff simultaneously with blood pressure measurement and is operator independent. PWV improves the calculation of CV risk.”
References


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