Ambulatory Systolic–Diastolic Pressure Regression Index as a Predictor of Clinical Events
A Meta-Analysis of Longitudinal Studies

Konstantinos Aznaouridis, MD*; Charalambos Vlachopoulos, MD*; Athanase Protogerou, MD; Christodoulos Stefanadis, MD

Background and Purpose—Blood pressure variables derived by ambulatory monitoring are important prognostic markers in hypertensive patients. Recent studies showed that ambulatory systolic–diastolic pressure regression index (ASDPRI), also known as ambulatory arterial stiffness index, may correlate with cardiovascular (CV) outcomes.

Methods—We explored the predictive value of ASDPRI for future CV events, stroke, and all-cause mortality by meta-analyses of 7 longitudinal studies that had evaluated ASDPRI and had followed 20,505 subjects for a mean follow-up of 7.8 years.

Results—The pooled relative risk of total CV events (including CV mortality), stroke, and all-cause mortality was 1.51 (95% CI, 1.18–1.93; \(P = 0.001\); 5 studies), 2.01 (95% CI, 1.60–2.52; \(P = 0.001\); 4 studies), and 1.25 (95% CI, 1.10–1.41; \(P = 0.001\); 4 studies), respectively, for high ASDPRI versus low ASDPRI subjects. An increase of ASDPRI by 1 standard deviation was associated with an age-adjusted, sex-adjusted, and risk factor-adjusted relative risk increase of total CV events and stroke by 15% and 30%, respectively. ASDPRI predicted stroke better than total CV events, predicted stroke better in normotensive subjects than in hypertensive patients, and also predicted total CV events better in females than in males. There was not significant publication bias.

Conclusions—ASDPRI is an ambulatory blood pressure-derived biomarker that strongly predicts future CV events, stroke, and all-cause mortality. These findings suggest that this index may be useful for risk stratification purposes. (Stroke. 2012;43:733-739.)

Key Words: ambulatory arterial stiffness index ■ ambulatory systolic–diastolic pressure regression index ■ arterial stiffness ■ cardiovascular risk ■ meta-analysis ■ prediction

Blood pressure (BP) variables derived by ambulatory BP recordings are important prognostic markers in hypertensive patients. A higher ambulatory systolic BP or diastolic BP predicts cardiovascular (CV) events in treated hypertensive patients, even after adjustment for office BP.1,2 Recently, a large epidemiological study showed that ambulatory systolic BP, and especially night-time pressure, is an important predictor of CV events and all-cause mortality.3

Ambulatory systolic–diastolic pressure regression index (ASDPRI) is a relatively novel index based on the relative behavior of 24-hour systolic BP and diastolic BP.4 ASDPRI is calculated as 1 minus the regression slope of the diastolic versus the systolic pressure from 24-hour BP recordings. ASDPRI has been proposed as a marker of arterial stiffness4 and, accordingly, it is commonly referred as ambulatory arterial stiffness index (AASI). However, the role of ASDPRI/AASI as an index of arterial stiffness has been questioned.5,6 Studies have shown that ASDPRI can vary considerably even for similar levels of the 24-hour ambulatory BP and pulse pressure, suggesting that ASDPRI might provide additional hemodynamic information.7 ASDPRI correlates with markers of preclinical target organ damage8 and, importantly, with CV outcomes,7,9–15 especially stroke.7,9,10,12,14 However, no overall quantitative estimate of this role exists. Furthermore, the studies that investigated the predictive role of ASDPRI have involved different populations, and thus have given rise to dissimilar risk estimates. In addition, because most studies that have been published have yielded positive results, publications bias may have been involved. Accordingly, we conducted the present meta-analysis with the aim to provide an overview of relevant studies and calculate robust quantitative estimates on the predictive value of ASDPRI for different outcomes, such as composite CV events, stroke, and all-cause mortality. Second, we investigated whether publication bias could have affected the true predictive ability of ASDPRI.
Table. Overview of Studies on the Association Between Ambulatory Systolic–Diastolic Pressure Regression Index and Clinical End Points

<table>
<thead>
<tr>
<th>Author, Y</th>
<th>Population Sample Size</th>
<th>Age (y)</th>
<th>Men (%)</th>
<th>Follow-up Duration</th>
<th>Events</th>
<th>Ambulatory Systolic–Diastolic Pressure Regression Index Cut-off (high vs Low)</th>
<th>Ambulatory Systolic–Diastolic Pressure Index Model</th>
<th>Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolan 2006</td>
<td>Hypertension (most) (N = 11291)</td>
<td>54.6 ± 14.6</td>
<td>47.2</td>
<td>5.3 y (median)</td>
<td>566 CV deaths (151 stroke deaths, 358 cardiac deaths)</td>
<td>Upper boundary of the 95 prediction interval of individual data points in relation to age</td>
<td>Continuous; dichotomous</td>
<td>Sex, age, MAP, BMI, smoking, diabetes, history of CVD</td>
</tr>
<tr>
<td>Hansen 2009</td>
<td>Community-based adults (half hypertensive) (N = 1829)</td>
<td>55.5 ± 10.7</td>
<td>53.1</td>
<td>9.4 y (median)</td>
<td>212 CV events (40 strokes, 150 CHD events)</td>
<td>As above</td>
<td>Continuous; dichotomous</td>
<td>Age, sex, BMI, MAP, smoking, diabetes, TC/HDL, history of CVD</td>
</tr>
<tr>
<td>Kikuya 2007</td>
<td>General population (half hypertensive) (N = 1542)</td>
<td>61.7 ± 10.7</td>
<td>36.6</td>
<td>13.3 y (median)</td>
<td>345 deaths (126 CV deaths, 63 stroke deaths)</td>
<td>Upper quartile compared with whole population</td>
<td>Dichotomous</td>
<td>Sex, age, 24-h MAP, BMI, smoking, alcohol, diabetes, history of CVD</td>
</tr>
<tr>
<td>Ben-Dov 2008</td>
<td>Hypertension (most) (N = 2918)</td>
<td>56 ± 16</td>
<td>45</td>
<td>7.0 y (mean)</td>
<td>215 deaths (all-cause)</td>
<td>Median</td>
<td>Continuous; median</td>
<td>Age, sex, 24-h SBP, treatment for hypertension and diabetes</td>
</tr>
<tr>
<td>Palmas 2009</td>
<td>Elderly with diabetes (N = 1178)</td>
<td>71 ± 6</td>
<td>40.6</td>
<td>6.6 y (mean)</td>
<td>287 deaths (110 CV deaths)</td>
<td>Upper vs lower tertile</td>
<td>Tertiles</td>
<td>age, sex, diabetes duration, smoking, CHF, MI, HDL, ACEI/ARB use, HR</td>
</tr>
<tr>
<td>Bastos 2010</td>
<td>Hypertension (N = 1200)</td>
<td>50.7 ± 12.7</td>
<td>46.2</td>
<td>8.2 y (mean)</td>
<td>62 deaths (152 CV events, 79 strokes)</td>
<td>Median</td>
<td>Continuous; median</td>
<td>Age, sex, diabetes, BMI, antihypertensive treatment</td>
</tr>
<tr>
<td>Murfeldt 2010</td>
<td>Resistant hypertension (N = 547)</td>
<td>65.9 ± 11.3</td>
<td>29.1</td>
<td>4.8 y (median)</td>
<td>65 deaths (45 CV deaths, 101 CV events)</td>
<td>Median</td>
<td>Continuous; median</td>
<td>Age, sex, BMI, DM, smoking, HDL, history of CVD, creatinine, N of antihypertensive medications, 24-h SBP–DBP</td>
</tr>
</tbody>
</table>

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CHD, coronary heart disease; CHF, congestive heart failure; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; HDL, high-density lipoprotein; HR, heart rate; MAP, mean arterial pressure; MI, myocardial infarction; SBP, systolic blood pressure; TC, total cholesterol.

Materials and Methods

Outcomes

The outcomes of interest were total CV events (CV deaths and nonfatal CV events, such as myocardial infarction, stroke, revascularization, aortic syndromes), stroke (fetal and nonfatal), and all-cause mortality.

Study Eligibility

Studies were deemed eligible if they: (1) were full-length publications in peer-reviewed journals; (2) evaluated ASDPRI/AASI; and (3) reported a combined CV outcome or CV mortality or myocardial infarction or stroke or all-cause mortality. No restriction criteria were imposed with regard to the type of the population, the size of the population, or the duration of follow-up.

Literature Search

Studies were drawn from a systematic review of the literature in PubMed and Cochrane database until June 2011. The search terms were: “ambulatory arterial stiffness” or “ambulatory arterial stiffness index” or “arterial stiffness” or “arterial elasticity” and “prediction” or “risk” or “death” or “mortality” or “outcome” or “events” or “stroke.”

Extraction of Data

The search of literature, selection of studies, and extraction of data were performed independently by 2 reviewers (K.A., C.V.). Disagreements were resolved by consensus. For each study, we recorded a risk estimate for ASDPRI. Numeric data appearing in the articles were used. In a few studies not reporting these data, we calculated risk estimates from the survival curves.

Statistical Analysis

The risk estimates of each study were reported as a hazard ratio, relative risk (RR), odds ratio, or dichotomous frequency data. We treated hazard ratios as RR. Because no uniform cut-off values are available for ASDPRI/AASI, patients were allocated to “high ASDPRI” or “low ASDPRI” groups according to cut-offs provided by each study (Table). When available, we used the adjusted risk estimates from multivariate models.

We obtained the pooled RR separately for total CV events, stroke, and all-cause mortality. The proportion of inconsistency across studies not explained by chance was quantified with the I² statistic. Heterogeneity between subgroups was calculated with Cochran Q test. 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. We also calculated adjusted RR per absolute ASDPRI difference (1 standard deviation) in addition to the calculation of RR of high versus low ASDPRI groups in each study. Finally, we performed sensitivity analysis to compare the strength of risk estimates between subgroups using a test of interaction. The RR and CI of comparable studies were illustrated with forest plots.

To estimate the contribution of continuous moderators on the overall heterogeneity, we performed meta-regression analyses with restricted maximum likelihood estimates. The presence of publication bias was investigated graphically by funnel plots of precision, and its implications were assessed by Duval and Tweedie trim-and-fill method and the classic fail-safe N method. All analyses were performed with Comprehensive Meta-Analysis version 2 (Biostat, Englewood, New Jersey).

Results

Qualitative Summary

Our search identified 58 publications, which were narrowed by preliminary review to 19 original articles. Further, articles were excluded because of cross-sectional study design or report of end points other than CV events, stroke, or death (N = 11). Eight studies measuring ASDPRI/AASI were deemed eligible for our meta-analysis. Of those...
studies\textsuperscript{12} provided risk estimates from a part of the population included in another study\textsuperscript{9} and was excluded. Finally, our meta-analysis included 7 original articles.\textsuperscript{7,9–11,13–15.}

In total, the included studies analyzed 20,505 subjects. Several populations (hypertensive, diabetic, general) were included. Details of the individual studies are shown in the Table. All studies were published since 2006 and the mean/median follow-up ranged from 4.8 years\textsuperscript{15} to 13.3 years\textsuperscript{10} (mean, 7.8 years). The sample sizes ranged from 547\textsuperscript{15} to 11,291 individuals.\textsuperscript{7}

All but 1 study\textsuperscript{11} assessed CV events, including CV mortality. In 3 studies,\textsuperscript{7,10,13} CV mortality was separately assessed, but data were not reported in 1 of those studies.\textsuperscript{13} Incidence of stroke was assessed in 4 studies.\textsuperscript{7,9,10,14} All-cause mortality was evaluated in 4 studies.\textsuperscript{10,11,13,15} Age, gender, and other risk factors for cardiovascular disease were controlled for in all studies (Table).

### Meta-Analysis

We performed separate meta-analyses for total CV events, stroke, and all-cause mortality. Pooled RR for high versus low aortic ASDPRI were calculated for all 3 outcomes. We also calculated pooled RR for increases of ASDPRI per 1 SD (total CV events and stroke).

#### Total CV Events

The risk in individuals with high ASDPRI was significantly higher compared to the risk of individuals with low ASDPRI. The pooled RR for high ASDPRI was 1.51 (95% CI, 1.18–1.93; \(P=0.001\)) for total CV events (Figure 1A). The pooled RR of total CV events for an increase of ASDPRI by 1 SD was 1.15 (95% CI, 1.08–1.24), corresponding to a risk increase of 15% (Figure 2A). Two studies\textsuperscript{10,15} provided data on CV events according to gender. In those studies, the pooled RR for high ASDPRI was higher in women than in men. The pooled RR for high versus low aortic ASDPRI were calculated for all 3 outcomes. We also calculated pooled RR for increases of ASDPRI per 1 SD (total CV events and stroke).

#### Figures

**Figure 1.** Relative risk (RR) and 95% confidence interval (CI) for high ambulatory systolic–diastolic pressure regression index (ASDPRI) and total cardiovascular (CV) events (A), stroke (B), and all-cause mortality (C). Studies are listed according to the date of publication. Boxes represent the RR and lines represent the 95% CI for individual studies. The diamonds and their width represent the pooled RR and the 95% CI, respectively. DM, diabetes mellitus; GEN, general population; HTN, hypertension.

**Figure 2.** Relative risk (RR) and 95% confidence interval (CI) for a 1-standard deviation increase in ambulatory systolic–diastolic pressure regression index (ASDPRI) and total cardiovascular (CV) events (A) and stroke (B). Studies are listed according to the date of publication. Symbols and abbreviations as in Figure 1.
men (1.59; 95% CI, 1.26–2.01 versus 0.96 and 95% CI, 0.70–1.30, respectively; \( P = 0.01 \) between the 2 gender comparisons).

**Stroke**

The pooled RR of stroke incidence was higher for high ASDPRI compared with low ASDPRI subjects (2.01; 95% CI, 1.60–2.52; \( P < 0.001 \); Figure 1B). The pooled RR of stroke incidence for an increase of ASDPRI by 1 SD was 1.30 (95% CI, 1.14–1.49; \( P < 0.001 \); Figure 2B), corresponding to a risk increase of 30%. Two studies\(^7,9\) provided stroke data according to the hypertension status. In those studies, the pooled RR for an increase of ASDPRI by 1 SD was higher in normotensive patients (1.87; 95% CI, 1.32–2.64 versus 1.13 and 95% CI, 0.94–1.35 in hypertensive patients; \( P = 0.012 \); Figure 3A). Data on stroke incidence according to gender were provided only in 1 study\(^9\) showing no independent interaction between gender and the predictive role of ASDPRI for stroke; thus, no meta-analysis could be performed to explore this relationship.

**Total CV Events Versus Stroke**

Four studies\(^7,9,10,14\) evaluated both total CV events and stroke. In those studies, the RR (high versus low ASDPRI) for stroke was higher compared to the RR for total CV events (2.01, 95% CI, 1.60–2.52 versus 1.49, 95% CI, 1.29–1.72; \( P = 0.029 \); Figure 3B), indicating that the ability of high ASDPRI is higher for stroke prediction than for total CV events prediction. The RR per 1-SD increase was higher for stroke than for total CV events, but this difference was not statistically significant (1.30 and 95% CI, 1.14–1.49 versus 1.13, 95% CI, 1.05–1.21; \( P = 0.065 \); Figure 3C).

**All-Cause Mortality**

The pooled RR of all-cause mortality was higher for high ASDPRI compared with low ASDPRI subjects (1.25; 95% CI, 1.10–1.41; \( P = 0.001 \); Figure 1C).

**Meta-Regression Analysis**

We performed a meta-regression analysis to estimate the impact of study moderators, like age and gender, on our estimates. Age did not correlate with any study outcome, which is an indirect indication that ASDPRI retains its predictive ability independently of age. There was an inverse association between the percentage of male gender and the RR of 1-SD increase of ASDPRI for total CV events (Figure 4), indicating that ASDPRI is a stronger determinant of future CV events in females. Analysis of 3 studies\(^7,9,14\) did not show any significant relationship between gender and the respective RR for stroke (\( P = 0.28 \)).

**Publication Biases**

**Studies Relating ASDPRI With Total CV Events**

The funnel plot was symmetrical (Figure 5A), suggesting an absence of significant publication bias. The trim-and-fill method did not impute any study, and our initial pooled risk estimate did not change. The fail-safe N was 41, which is
reassuring. The fail-safe N test computes the number of the theoretically missing studies (with mean effect of zero) that would need to be added to the analysis to yield a statistically nonsignificant overall effect, and it is unlikely that there are >8.2 (41/5 = 8.2) unpublished or undiscovered studies for every 1 study we found. These findings suggest that the apparent publication bias is insufficient to affect our results or interpretations in a meaningful way.

**Studies Relating ASDPRI With Stroke**

This funnel plot was slightly asymmetrical (Figure 5B), suggesting an absence of studies with small or negative risk estimates either because of publication bias or because of a true inexistence of negative studies (absence of publication bias). The trim-and-fill method imputed missing studies and recalculated our pooled risk estimate. The imputed RR was 1.74 (95% CI, 1.44–2.11), which is lower than our original risk estimate but is still a significant one. The fail-safe N was 36, which is reassuring because it is very unlikely that there are >9 (36/4 = 9) unpublished or undiscovered studies for every 1 study we found.

**Studies Relating ASDPRI With All-Cause Mortality**

The funnel plot was slightly asymmetrical (Figure 5C). The fail-safe N was 9, which is not reassuring, because it is not unlikely that there are over >2.25 (9/4 = 2.25) unpublished or undiscovered studies for every 1 study we found. However, the trim-and-fill method showed an imputed RR of 1.20 (95% CI, 1.07–1.34), which remains significant. These findings suggest that the apparent publication bias is insufficient to affect our results or interpretations in a meaningful way.

**Discussion**

In this systematic review and meta-analysis, we pooled ASDPRI data of 20,505 subjects from 7 studies who were followed-up for a mean of 7.8 years. The risk of CV events, stroke, and all-cause mortality in subjects with increased ASDPRI was significantly higher compared to the risk of subjects with lower ASDPRI. Importantly, the predictive value of increased ASDPRI for stroke was considerably higher than the predictive value for total CV events and all-cause death. Finally, the ability of ASDPRI to predict stroke was better in subjects without hypertension, whereas its ability for total CV events prediction was better in females.

This is the first meta-analysis to our knowledge to provide robust pooled estimates on the role of ASDPRI for risk prediction. A strength of our study is the exhaustive search strategy that likely enabled us to capture most, if not all, relevant studies. Furthermore, we dealt with potential publication bias. The fact that there are not many published studies with negative results may be attributable to a true “universal” predictive role of ASDPRI or may reflect publication biases. Even if the latter is the case, our analysis (using 2 approaches, the trim-and-fill and fail-safe N methods) indicates that any publication biases may have accounted only for a slight overestimation of the true predictive role of ASDPRI.

Although the ability of ASDPRI to predict clinical events appears indisputable, the pathophysiological background of this relationship remains unclear. In most studies, ASDPRI is considered a measure of arterial stiffness. The proposed rationale underlying this relationship is that for any given increase in distending BP, systolic and diastolic BP tend to increase in a parallel fashion in a compliant artery, whereas in a stiff artery the increase in systolic pressure is accompanied by a lesser increase, or even by a decrease, in diastolic

![Figure 5.](http://stroke.ahajournals.org/Downloaded from http://stroke.ahajournals.org)
pressure. The study of Li et al., one of the seminal studies on ASDPRI, showed that ASDPRI correlates well with aortic pulse wave velocity, which is the gold standard of large arteries stiffness, and reinforced this notion. However, other studies did not confirm the association between ASDPRI and pulse wave velocity. Furthermore, the other seminal study of Dolan et al. demonstrated that ASDPRI can be quite similar in patients with considerable differences in the absolute levels of their 24-hour ambulatory BP. This contrasts, to some extent, the well-established notion that higher BP is usually associated with an increase of arterial stiffness and questions whether ASDPRI is a marker of “genuine stiffness.” Recent data show that ASDPRI is significantly influenced by the range of variation in diastolic BP over the 24 hours and the nocturnal BP decline (dipping status) and can vary considerably even in subjects with similar levels of blood pressure. Taken together, these data imply that ASDPRI may reflect complex cardiovascular regulatory mechanisms beyond arterial stiffness, such as total peripheral resistance, baroreceptor sensitivity, and arterio-ven- tricular coupling. Therefore, although the predictive role of arterial stiffness is well-established, it is unclear whether ASDPRI is a reliable measure of arterial stiffness. Undoubtedly, further studies are needed to explore the pathophysiological relationship of ASDPRI with arterial stiffness and to compare it with established stiffness indices in terms of cardiovascular risk prediction.

Our findings suggest that the ability of ASDPRI to predict stroke is higher than its ability for total CV events and all-cause death prediction. It seems that ASDPRI is more representative of the effects of BP and other CV risk factors on the cerebral circulation than the other vascular beds. Explanations may include a preferential relation of the steady rather than the pulsatile component of BP with prediction of stroke; ASDPRI correlates well and independently with the mean pressure, which reflects the steady component. Interestingly, the predictive ability of ASDPRI for stroke was significantly higher in nonhypertensive populations. Recent data show that antihypertensive treatment, which is well-known to improve prognosis in hypertensive patients, does not modify ASDPRI. In contrast, arterial stiffness, an important predictor of events in hypertensive patients, improved significantly with antihypertensive drugs in that study. Taken together, although no direct pathophysiological explanation exists, these data imply that ASDPRI may not be an ideal risk predictor in hypertensive patients.

Furthermore, we observed that the ability of ASDPRI for total CV events prediction may be higher in women than in men. In contrast, our analysis did not confirm any association between gender and the role of ASDPRI for stroke prediction. As ASDPRI reflects both steady (diastolic) and pulsatile (systolic) components of BP, potential explanations may include a preferential predictive role of the pulsatile component for myocardial infarction, not stroke, only in women, not in men. However, because our finding of a more prominent role of ASDPRI for CV events prediction in women is based on few studies only and because a clear pathophysiological explanation is lacking, further research is needed.

We acknowledge the limitation that 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 ASDPRI is independent of BP, its ability to discriminate, calibrate, and reclassify risk could not be assessed because the studies we included do not provide such data. To define high and low ASDPRI, we used the cut-off values used by each study because there are no established cut-offs. This may have theoretically introduced a bias. Because of the small number of relevant studies in the literature, our study is not powered to explain possible heterogeneity between original studies, so further original studies are needed.

Conclusions

Our meta-analysis shows that ASDPRI predicts independently future clinical events. Its predictive ability is better for stroke than for other CV events or all-cause death. ASDPRI is a better risk predictor of stroke in normotensive subjects than in hypertensive populations, whereas its ability for total CV events prediction seems to be better in females. Whether a pathophysiological and clinical correlate of arterial stiffness, ASDPRI shows 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 ASDPRI to discriminate, calibrate, and reclassify the risk of patients.

Disclosures

None.

References

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