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.
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.6–15 One of those
studies provided risk estimates from a part of the population included in another study and was excluded. Finally, our meta-analysis included 7 original articles. 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 to 13.3 years (mean, 7.8 years). The sample sizes ranged from 547 to 11,291 individuals.

All but 1 study assessed CV events, including CV mortality. In 3 studies, CV mortality was separately assessed, but data were not reported in 1 of those studies. Incidence of stroke was assessed in 4 studies. All-cause mortality was evaluated in 4 studies. 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 provided data on CV events according to gender. In those studies, the pooled RR for high ASDPRI was higher in women than in men.

---

**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 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 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 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 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

---

**Figure 3.** Relative risk (RR) and 95% confidence interval (CI) of stroke for a 1-standard deviation increase in ambulatory systolic–diastolic pressure regression index (ASDPRI) according to the hypertension status (A). RR and 95% CI for ASDPRI, according to the outcome (total cardiovascular [CV] events vs stroke) for high vs low aortic ASDPRI (B) and for a 1-standard deviation increase in ASDPRI (C). Symbols as in Figure 1.

**Figure 4.** Logarithm of relative risk (RR) of total cardiovascular (CV) events for 1-standard deviation increase in ambulatory systolic–diastolic pressure regression index (ASDPRI) as a function of the percentage of males in the studies. The size of the data markers relates to the weight of each study.
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 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
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-ventricular 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 setting. Hence, 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.

**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**


Ambulatory Systolic–Diastolic Pressure Regression Index as a Predictor of Clinical Events: A Meta-Analysis of Longitudinal Studies
Konstantinos Aznaouridis, Charalambos Vlachopoulos, Athanase Protogerou and Christodoulos Stefanadis

*Stroke*. 2012;43:733-739; originally published online January 26, 2012;
doi: 10.1161/STROKEAHA.111.636688

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/43/3/733

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/