

# 24-Hour Blood Pressure Variability Assessed by Average Real Variability: A Systematic Review and Meta-Analysis

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**Background**—Although 24-hour blood pressure (BP) variability (BPV) is predictive of cardiovascular outcomes independent of absolute BP levels, it is not regularly assessed in clinical practice. One possible limitation to routine BPV assessment is the lack of standardized methods for accurately estimating 24-hour BPV. We conducted a systematic review to assess the predictive power of reported BPV indexes to address appropriate quantification of 24-hour BPV, including the average real variability (ARV) index.

**Methods and Results**—Studies chosen for review were those that presented data for 24-hour BPV in adults from meta-analysis, longitudinal or cross-sectional design, and examined BPV in terms of the following issues: (1) methods used to calculate and evaluate ARV; (2) assessment of 24-hour BPV determined using noninvasive ambulatory BP monitoring; (3) multivariate analysis adjusted for covariates, including some measure of BP; (4) association of 24-hour BPV with subclinical organ damage; and (5) the predictive value of 24-hour BPV on target organ damage and rate of cardiovascular events. Of the 19 assessed studies, 17 reported significant associations between high ARV and the presence and progression of subclinical organ damage, as well as the incidence of hard end points, such as cardiovascular events. In all these cases, ARV remained a significant independent predictor ( $P < 0.05$ ) after adjustment for BP and other clinical factors. In addition, increased ARV in systolic BP was associated with risk of all cardiovascular events (hazard ratio, 1.18; 95% confidence interval, 1.09–1.27). Only 2 cross-sectional studies did not find that high ARV was a significant risk factor.

**Conclusions**—Current evidence suggests that ARV index adds significant prognostic information to 24-hour ambulatory BP monitoring and is a useful approach for studying the clinical value of BPV. (*J Am Heart Assoc.* 2017;6:e006895. DOI: 10.1161/JAHA.117.006895.)

**Key Words:** blood pressure variability • cardiovascular events • target organ damage

**B**lood pressure (BP) is a dynamic physiological parameter, influenced by behavioral, emotional, and environmental factors, as well as intrinsic cardiovascular control. Daily variation in BP is the sum of responses to extrinsic pressor stimuli, spontaneous and regulatory fluctuations attributable to influences of the central nervous system,<sup>1,2</sup> mechanical forces generated by respiration,<sup>3</sup> and effects of humoral and

local vasomotor phenomena.<sup>4,5</sup> Regardless of the causes, arterial and cardiopulmonary reflexes act as modulators of short-term changes in BP. Reduced efficacy of those reflexes can result in significant increases in BP oscillations.<sup>6,7</sup> Within-subject BP variability (BPV) also increases with elevated average BP and age.<sup>8,9</sup> The clinical relevance of BPV during a 24-hour period was initially examined through intra-arterial beat-to-beat measurements.<sup>9–11</sup> Early studies showed that increased BPV in hypertensive individuals is directly related to severity of target organ damage.<sup>10–12</sup> Later studies, using noninvasive, intermittent, reading-to-reading, 24-hour ambulatory BP monitoring (ABPM), provided evidence that an initial increase in BPV is an independent predictor of cardiovascular events/complications.<sup>13–16</sup> However, despite evidence of the clinical relevance of BPV, its pathological role remains a hypothesis, and it is not regularly used in clinical practice. One possible limitation to routine BPV assessment is the lack of standardized methods for accurately estimating 24-hour BPV.<sup>17,18</sup>

The clinical significance and prognostic implications of BPV depend on the measurement method<sup>6,19</sup> and sampling frequency.<sup>17–20</sup> Most studies have evaluated the predictive

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Received June 8, 2017; accepted August 29, 2017.

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## Clinical Perspective

### What Is New?

- Until now, there has not been a systematic review or meta-analysis comparing the prognostic value of the different indexes used to measure 24-hour blood pressure (BP) variability.
- Average real variability was a better estimator of 24-hour BP variability than other measures of dispersion. Average real variability remained as an independent predictor after adjustment for BP and other clinical factors for the presence and progression of subclinical organ damage. Incidences of cardiovascular events in the general population and hypertensive individuals were considered.

### What Are the Clinical Implications?

- The average real variability index adds significant prognostic information to 24-hour ambulatory BP monitoring, and is a useful approach for studying the clinical value of BP variability. However, further investigation is required to define potential diagnostic thresholds of abnormal BP variability before this parameter becomes a regular tool for clinical use.

value of BPV based on the SD of 24-hour average ABPM recordings, but this index is an approximate indicator of BP dynamics and does not capture many characteristics of BPV.<sup>21–23</sup> Because the SD is correlated with mean BP, it can be inadequate to use both measurements in a multivariate prognostic model.<sup>24</sup> One solution is to use the coefficient of variation (CV),<sup>25</sup> which is the SD divided by the corresponding mean; or to calculate the variation independent of mean,<sup>26</sup> which is similar to the CV, but with the mean raised to a power,  $x$ , that removes the correlation. Another important limitation of the 24-hour SD is that its magnitude is significantly affected by the nocturnal BP decrease in individuals with large daily fluctuations.<sup>27,28</sup> This “dipping” phenomenon can reduce the prognostic power of 24-hour SD.<sup>21</sup> Calculation of a “weighted” 24-hour SD (wSD; computed as the average of day and night SDs, weighted for their respective durations) can minimize the effect of nocturnal dipping without discarding information about BPV.<sup>28,29</sup>

Hypertensive individuals are generally characterized by steep, rapid, short-duration BPV that might have clinical implications.<sup>30,31</sup> However, the SD does not reflect the steepness or rapidity. Therefore, the time rate of BP variation (TRBPV) was proposed as an alternative index by Zakopoulos et al.<sup>32</sup> The TRBPV measures the steepness and speed of changes in BP, calculated as the mean of the absolute ratios of the difference between successive BP readings and the time between them.

To improve the predictive power of 24-hour BPV, Mena et al proposed the average real variability (ARV) index.<sup>33</sup> This method focuses on changes occurring over short time intervals and, thus, corrects some of the limitations of SD, which only reflects the dispersion of BP measurements around the mean. The ARV index calculates the average of absolute changes between consecutive BP readings:

$$ARV = \frac{1}{N-1} \sum_{k=1}^{N-1} |BP_{k+1} - BP_k|$$

where  $N$  denotes the number of valid BP measurements, and  $k$  is the order of measurements. Mena et al<sup>33</sup> concluded that the ARV index has a greater predictive value than the SD and is more useful for determining therapeutic measures aimed at controlling BPV. However, the relatively high event rate observed in that study indicated that its results could not be completely extrapolated to the general population of hypertensive subjects, and that further study of the prognostic significance of the ARV index was required.<sup>21</sup>

This review systematically examines recent studies of the ARV index and its prognostic value, specifically its association with subclinical target organ damage and the incidence of cardiovascular events in the general population and hypertensive individuals. We critically discuss the methods that should be considered for standardized estimation of 24-hour BPV and other fundamental issues that need to be addressed before this parameter becomes a regular tool for clinical use.

## Methods

Only original publications in English language were considered. The quality of the relevant articles was assessed using the guidelines recommended by Hayden et al.<sup>34</sup>

One author (V.G.F.) performed a literature search of potentially relevant articles in the PubMed/MEDLINE database using the keywords “ARV,” “average,” “real,” “blood pressure,” and “variability” and in Google Scholar service based on publications that cited Mena et al<sup>33</sup> (up to July 2016). Two authors (V.G.F., J.D.M.) reviewed the abstracts and titles to identify relevant articles, and disagreements were resolved by discussion and debate with a third author (L.J.M.). The full texts of selected articles were obtained, and data were extracted, verified, and checked independently by 2 authors (L.J.M., G.E.M.). Discrepancies were discussed to reach a consensus.

The studies chosen for review were those that presented data for 24-hour BPV in adults from meta-analysis, longitudinal or cross-sectional design, and examined BPV in terms of the following issues: (1) method used to calculate and evaluate ARV; (2) assessment of 24-hour BPV, determined using noninvasive ABPM; (3) multivariate analysis adjusted for covariates, including some measure of BP; (4) association of

24-hour BPV with subclinical organ damage; and (5) the predictive value of 24-hour BPV on target organ damage and rate of cardiovascular events.

Data extracted from the reviewed studies included the type of population, study design, sample size, sex distribution, mean age, BPV indexes, confounding variables included in multivariate analyses, and minimum number of valid BP readings used to quantify BPV. For studies with several multivariate analyses, we focused on fully adjusted models that included BP as a predictor variable to avoid selection bias. Only significant BPV predictors ( $P < 0.05$ ) were selected to address independent risk contribution of BP variation over and above the influence of elevated mean BP levels. When the minimum number of 24-hour BP readings was not specified, approximate values were estimated on the basis of sampling interval and quality criteria defined by authors or assumed to be 80% of the maximum possible BP measurements.

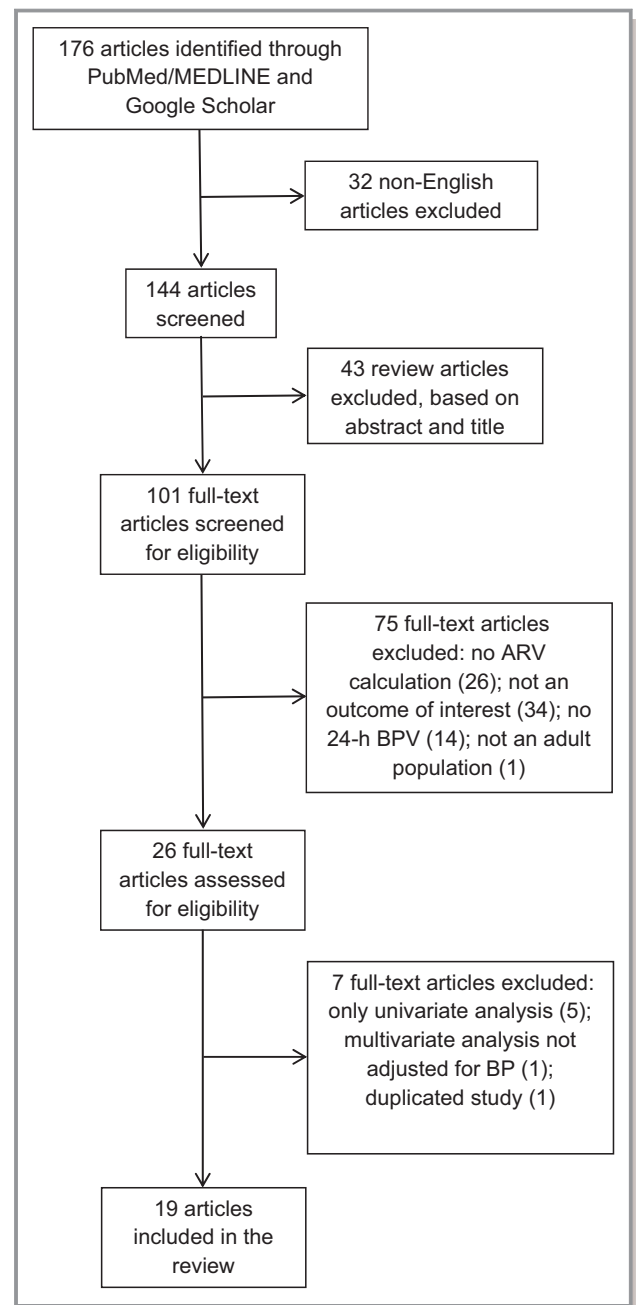
Data from long-term prognostic fatal and nonfatal cardiovascular events were pooled using a random-effects meta-analysis. Only studies that provided hazard ratios were included in this analysis. Heterogeneity was assessed using the  $\chi^2$  test and  $I^2$  statistic.<sup>35</sup> The Egger test<sup>36</sup> was used to assess the extent of publication bias.  $P < 0.10$  was considered as heterogeneity and asymmetry between studies.

## Results

The initial search identified 176 articles citing the article by Mena et al (Figure 1).<sup>33</sup> On the basis of our criteria, 157 were excluded, leaving 19 articles in our systematic review. All studies received ethical approval, and each participant gave informed consent. Ten of these<sup>37–46</sup> investigated the prognostic value of 24-hour BPV (Table 1). Nine studies<sup>47–55</sup> examined its relation to target organ damage (cardiac, cerebral, arterial, renal, endothelial, and vascular).

The design of the 19 studies included 2 meta-analyses,<sup>37,38</sup> 3 prospective studies,<sup>39–41</sup> and 14 cross-sectional studies.<sup>42–55</sup> Sample sizes ranged from 36<sup>52,54</sup> to 8938<sup>37</sup> individuals, and the study populations included European, Asian, and North American cohorts, as well as compounded international databases. Eight studies focused on hypertensive populations,<sup>40,42–45,48,49,55</sup> and 3 of those included patients with diabetes mellitus<sup>48</sup> or chronic kidney disease.<sup>44,55</sup> The remaining studies involved healthy subjects,<sup>52,53</sup> populations with mixed hypertensive status,<sup>39,50,51,54</sup> or subjects drawn from the general population.<sup>37,38,41,46,47</sup>

Analytical approaches used by the 19 studies included multivariate analyses using Cox,<sup>37–40</sup> logistic,<sup>41–46</sup> or linear<sup>47–55</sup> regression models, which incorporated ARV as an independent variable. Six studies used ARV as a unique index for



**Figure 1.** Flow chart showing the process for selection of articles. ARV indicates average real variability; BP, blood pressure; and BPV, BP variability.

estimating BPV.<sup>38,39,44,53–55</sup> In addition to ARV, 10 studies included measures of dispersion, such as SD,<sup>37,40–43,45–49</sup> CV,<sup>41,42,46,47</sup> and wSD.<sup>37,41–43,45–47</sup> Three studies used alternative indexes, such as variation independent of mean<sup>50</sup> or TRBPV,<sup>51,52</sup> to assess BPV. The estimated minimum number of BP measurements required for accurate estimates of ARV ranged from 15<sup>37</sup> to 77.<sup>49</sup> The mean of the minimum sampling rate was of  $42.9 \pm 16.7$  BP readings.  $P < 0.05$  was considered statistically significant in all cases.

**Table 1.** Studies That Assessed the Prognostic Value of ARV by Multivariate Analysis

Study	Population	Design	N, (Women, %)	Age, Mean±SD, y	Estimated Minimum of BP Readings (↑/↓)	Outcome Measure	Significant BVP Index	Confounding Variables Included in Multivariate Analyses
Hansen et al <sup>37</sup>	General	Meta-analysis	8938 (46.8)	53.0±15.8	15 (↓)	Cardiovascular events	ARV, wSD	Age, sex, 24-h HR, BMI, smoking, drinking, TC, history of CVD, DM, TAD, corresponding 24-h BP level
Mena et al <sup>38</sup>	General	Meta-analysis	5343 (45.6)	54.0±16.1	48 (↑)	Cardiovascular events	ARV	Age, sex, BMI, smoking, drinking, TC, history of CVD, TAD, corresponding 24-h BP level
Hsu et al <sup>39</sup>	Normotensive and untreated hypertensive patients	Longitudinal	1257 (46.8)	53.1±13.1	42 (↓)	Cardiovascular events	ARV	Age, sex, smoking, TC, HDL-C, IFG, office SBP
Pierdomenico et al <sup>40</sup>	Untreated and treated hypertensive patients	Longitudinal	1280 (51.0)	58.0±10.0	59 (↑)	Cardiovascular events	ARV	Age, DM, LVH, daytime SBP level
Yamaguchi et al <sup>41</sup>	General	Longitudinal	210 (55.2)	70.9±0.9	27 (↓)	CSVD	ARV, wSD	Age, sex, hypertension, hyperlipidemia, DM, IGT, or IFG, 24-h SBP level
Filomena et al <sup>42</sup>	Asymptomatic hypertensive patients	Cross-sectional	487 (46.8)	64.0±3.0	47 (↑)	CSVD	ARV	Age, sex, DM, waist circumference, TAD, office DBP, corresponding SBP level
Leoncini et al <sup>43</sup>	Untreated hypertensive patients	Cross-sectional	169 (33.1)	47.1±9.5	64 (↑)	Multiple OD (GFR, IMT, LVH)	ARV, SD, wSD	Age, sex, BMI, smoking, triglycerides, LDL-C, glucose, SBP load
Madden et al <sup>46</sup>	General	Cross-sectional	1134 (53.5)	60.2±5.5	27 (↓)	Multiple OD (LVH, MAU)	Not significant	Age, sex, smoking, BMI, DM, TAD, 24-h SBP level
Ryu et al <sup>44</sup>	Hypertensive patients with CKD	Cross-sectional	1173 (37.0)	56.6±11.9	28 (↓)	LVH	ARV	Age, sex, smoking, DM, TAD, exercise, GFR, proteinuria, 24-h SBP level
Mulè et al <sup>45</sup>	Untreated hypertensive patients	Cross-sectional	315 (58.4)	45.2±12.4	70 (↑)	MAU	ARV	Age, sex, BMI or waist circumference, uric acid, DM or glucose, 24-h SBP level

↑, indicates number of BP readings above the minimum sampling rate; ↓, number of BP readings below the minimum sampling rate; ARV, average real variability; BMI, body mass index; BP, blood pressure; BPV, BP variability; CKD, chronic kidney disease; CSVD, cerebral small-vessel disease; CVD, cardiovascular disease; DBP, diastolic BP; DM, diabetes mellitus; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IMT, intima-media thickness; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; MAU, microalbuminuria; OD, organ damage; SBP, systolic BP; TAD, treatment with antihypertensive drug; TC, total cholesterol; and wSD, weighted SD.



## Prognostic Significance of ARV

Four studies examined the long-term prognostic significance of 24-hour BPV, estimated using ARV, for cardiovascular outcome<sup>37–40</sup> (Table 2). Two of the studies used large samples from the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome and combined results across cohorts in fully adjusted models.<sup>37,38</sup> The results showed that ARV, SD, and wSD predicted cardiovascular mortality over a median of 11.3 years of follow-up.<sup>37</sup> ARV and wSD predicted all fatal plus nonfatal cardiovascular outcomes. ARV predicted fatal outcomes plus nonfatal stroke. The authors concluded that ARV was a better predictor than SD and wSD for most outcomes and, thus, might be a more accurate measure of BPV than SD.<sup>37</sup> A later International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome study that used a minimum of 48 BP readings similarly found that ARV was a significant and independent predictor of cardiovascular and cardiac deaths and all cerebrovascular events.<sup>38</sup>

Hsu et al investigated the prognostic value of a high BPV in normotensive and hypertensive subjects over a median follow-up of 20 years.<sup>39</sup> The results showed that ARV predicted cardiovascular mortality independent of conventional risk factors plus office BP. ARV was not a significant predictor when 24-hour BP was included in the multivariable models. However, in subgroup analysis, ARV significantly predicted cardiovascular deaths in subjects with hypertension, independently of 24-hour mean BP and in addition to well-known risk factors. The authors concluded that BPV might be more useful than BP in long-term risk stratification for untreated hypertensive subjects. Pierdomenico et al also evaluated the independent prognostic significance of SD and ARV as indexes of BPV in initially untreated and treated hypertensive patients.<sup>40</sup> Multivariate analysis adjusted for

other covariates, including BP, showed that ARV as either a categorical or a continuous variable was an independent predictor of cardiovascular events, whereas SD was not. The authors concluded that ARV could be a more appropriate index of BPV than SD and a more useful predictor of outcomes.

Two studies evaluated the prognostic capacity of different BPV parameters (SD, CV, wSD, and ARV) as risk factors for cerebral small-vessel disease (CSVD), an important contributor to stroke and cognitive decline in elderly patients.<sup>56</sup> Yamaguchi et al conducted a 4-year, community-based, longitudinal study to determine whether CSVD progression was independently related to BPV.<sup>41</sup> Multivariable logistic regression analysis using BPV as a continuous variable showed that ARV and wSD were independent predictors of CSVD progression after adjustment for confounding factors and mean BP. The study also found that lacunar infarction was significantly associated with cognitive impairment and that only ARV differed significantly between subjects with and without cognitive decline. Similarly, Filomena et al conducted a cohort study on asymptomatic hypertensive patients to evaluate the potential usefulness of BPV as a predictor of CSVD, compared with BP and other clinical factors.<sup>42</sup> Only BPV, measured as ARV, was independently related to the presence of CSVD. Furthermore, ARV was the only metric significantly associated with lacunar brain infarcts and periventricular and deep white matter hyperintensities.

Four cross-sectional studies examined the predictive relationship of BPV to the development of organ damage. Leoncini et al assessed the independent influence of BPV on multiple target organ damage, including left ventricular hypertrophy, carotid atheromatosis, and renal abnormalities.<sup>43</sup> High BPV, measured as SD, wSD, and ARV, was associated with the simultaneous presence of 2 or more signs of subclinical organ damage, regardless of several confounding variables, including BP. Other multicenter studies of patients with hypertensive chronic kidney disease showed that ARV was an independent predictor of left ventricular hypertrophy, after adjustment for 24-hour mean BP and other factors.<sup>44</sup> In a study of BPV as a predictor of renal complications, multiple logistic regression analysis revealed that the presence of microalbuminuria was independently associated with ARV, after adjustment for average BP value and other potential confounders.<sup>45</sup> When ARV was replaced by SD or wSD in the same model, BPV was not independently associated with microalbuminuria. When the independent correlates of urinary albumin excretion rate were explored using stepwise linear multiple regression analysis, only ARV was significantly related to the outcome variable. In contrast, Madden et al found no significant correlations of BPV (SD, CV, wSD, and ARV) with left ventricular hypertrophy in both unadjusted and fully adjusted models. The association

**Table 2.** Multivariable-Adjusted Standardized HRs Associated With Higher Systolic ARV as a Continuous Variable

Study	Cardiovascular Outcome	No. of Events	Median Follow-Up, y	Systolic ARV HR (95% CI)
Hansen et al <sup>37</sup>	Fatal and nonfatal	1049	11.3	1.07 (1.00–1.48)*
Mena et al <sup>38</sup>	Fatal	335	10.2	1.17 (1.04–1.31)†
Hsu et al <sup>39</sup>	Fatal	90	20.0	1.20 (1.00–1.45)*
Pierdomenico et al <sup>40</sup>	Fatal and nonfatal	104	4.8	1.27 (1.06–1.51)*

Standardized HRs (95% CIs) were associated with a 1-SD increase in ARV for cardiovascular events by fully adjusted Cox proportional hazards regression models. ARV indicates average real variability; CI, confidence interval; and HR, hazard ratio.

\* $P < 0.05$ , HR significance.

† $P < 0.01$ , HR significance.

**Table 3.** ORs of Higher Systolic ARV for Progression of Target OD

Study	Outcome Measure	Systolic ARV OR (95% CI)
Yamaguchi et al <sup>41</sup>	CSVD	2.05 (1.04–4.03)*
Filomena et al <sup>42</sup>	CSVD	1.16 (1.02–1.33)*
Leoncini et al <sup>43</sup>	Multiple OD	1.14 (1.00–1.29)*
Ryu et al <sup>44</sup>	LVH	1.05 (1.02–1.09) <sup>†</sup>
Mulè et al <sup>45</sup>	MAU	5.34 (1.23–23.10)*

ORs (95% CIs) per 1-mm Hg increase in ARV by a fully adjusted multivariate logistic regression model. ARV indicates average real variability; CI, confidence interval; CSVD, cerebral small-vessel disease; LVH, left ventricular hypertrophy; MAU, microalbuminuria; OD, organ damage; and OR, odds ratio.

\* $P < 0.05$ , OR significance.

<sup>†</sup> $P < 0.01$ , OR significance.

between BPV and microalbuminuria did not persist for all indexes when mean BP was added to the model.<sup>46</sup> However, a subanalysis that included only subjects taking antihypertensive treatment showed a significant association between ARV and microalbuminuria, after adjustment for all confounders, including mean BP. Table 3 shows odds ratios of studies that determined that BPV assessed with ARV was an independent predictor of organ damage.

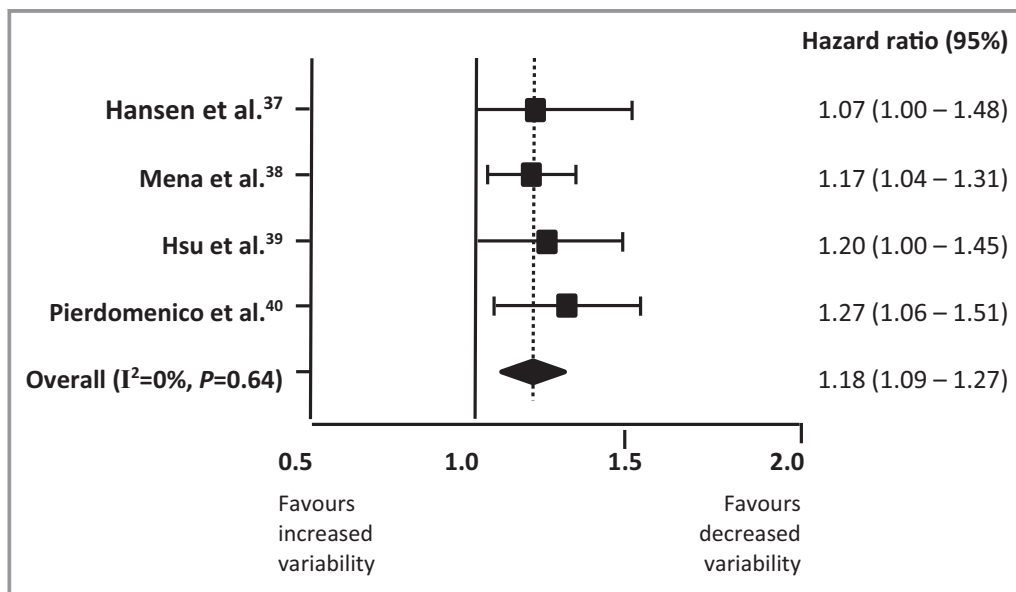
## Meta-Analysis

Figure 2 presents random-effects meta-analysis of hazard ratios for increases in systolic ARV and all cardiovascular events. Four studies that examined incidence of hard end points show a significant association (hazard ratio, 1.18; 95%

confidence interval, 1.09–1.27;  $I^2=0.0\%$ ;  $P=0.64$ ). The Egger test indicated no evidence of publication bias ( $P=0.95$ ).

## Association of ARV With Target Organ Damage

Nine studies evaluated the correlations between BPV and target organ damage (Table 4). Two studies examined carotid artery alteration, using carotid intima-media thickness as a sign of early atherosclerosis. Xiong et al found that ARV generally had a stronger relationship than SD or CV to intima-media thickness.<sup>47</sup> Comparison on the BPV parameters in a mixed model with backward selection regression showed that only ARV maintained a significant relationship to intima-media thickness, which remained significant after adjustment for baseline characteristics and mean BP. Wu et al concluded that ARV had greater prognostic significance than SD for evaluating the carotid intima-media thickness in hypertensive patients with diabetes mellitus.<sup>48</sup> Another study found that ARV had the strongest relationship to arterial stiffness, followed by the wSD and SD, after adjustment for age, sex, and 24-hour BP.<sup>49</sup> This result was confirmed through stepwise multiple linear regression analysis, showing the relationship between ARV and arterial stiffness was independent from, and in addition to, office BP and average 24-hour BP. In contrast, Wei et al found no significant association between BPV and 3 indexes of organ damage, except for an increase in aortic pulse wave velocity with increasing variation independent of mean and increasing difference between maximum and minimum BP.<sup>50</sup> However, the same study used the beat-to-beat recordings method and found that the left ventricular mass index was related to ARV, variation independent of



**Figure 2.** Random-effects meta-analysis of hazard ratios for increases of systolic average real variability and all cardiovascular events.

**Table 4.** Studies That Assessed the Association of ARV With Target OD by Multivariate Analysis

Study	Population	Design	N, (Women, %)	Age, Mean±SD, y	Estimated Minimum of BP Readings (↑/↓)	Outcome Measure	Significant BVP Index	Confounding Variables Included in Multivariate Analyses
Wei et al <sup>50</sup>	Normotensive and untreated hypertensive patients	Cross-sectional	256 (50.4)	51.1±10.3	45 (↑)	Multiple OD (LVH, MAU, PWV)	VIM, MMD	Age, sex, BMI, 24-h HR, smoking, drinking, TC, glucose, 24-h SBP level
Xiong et al <sup>47</sup>	General	Cross-sectional	60 (46.7)	58.7±12.1	38 (↓)	IMT	ARV, SD, CV	Age, sex, smoking, hypertension, corresponding PP and BP level
Wu et al <sup>48</sup>	Treated hypertensive patients with and without DM	Cross-sectional	148 (40.7)	57.7±13.0	38 (↓)	IMT	ARV	Age, sex, smoking, heart disease, 24-h and daytime DBP level
Schillaci et al <sup>49</sup>	Untreated hypertensive patients	Cross-sectional	911 (52.0)	49.0±11.0	77 (↑)	PWV	ARV	Age, HR, GFR, IFG, office SBP, 24-h SBP level
Diaz et al <sup>51</sup>	Normotensive or prehypertensive patients	Cross-sectional	38 (86.8)	52.6±1.5	32 (↓)	GFR	ARV, TRBPV	Age, BMI, 24-h DBP level
Ozkeyar et al <sup>55</sup>	Hypertensive renal transplant recipients	Cross-sectional	73 (28.8)	42.3±12.4	62 (↑)	Endothelial dysfunction	ARV	Age, sex, corresponding BP level
Diaz et al <sup>52</sup>	Nondiabetic, nonsmoking, and free of renal disease and CVD	Cross-sectional	36 (75.0)	52.0±1.0	32 (↓)	Endothelial dysfunction	ARV, TRBPV	Age, sex, BMI, corresponding 24-h BP level
Diaz et al <sup>53</sup>	Nondiabetic, nonsmoking, and free of CVD	Cross-sectional	72 (83.3)	51.7±0.7	32 (↓)	Smooth muscle function	ARV	Age, sex, BMI, corresponding 24-h BP level
Veerabhadrappa et al <sup>54</sup>	Normotensive or prehypertensive patients	Cross-sectional	36 (83.3)	52.0±7.0	32 (↓)	Circulating inflammatory markers	ARV	Age, sex, BMI, 24-h SBP level

↑, indicates number of BP readings above the minimum sampling rate; ↓, number of BP readings below the minimum sampling rate; ARV, average real variability; BMI, body mass index; BP, blood pressure; BPV, BP variability; CV, coefficient of variation; CVD, cardiovascular disease; DBP, diastolic BP; DM, diabetes mellitus; GFR, glomerular filtration rate; HR, heart rate; IFG, impaired fasting glucose; IMT, intima-media thickness; LVH, left ventricular hypertrophy; MAU, microalbuminuria; MMD, difference between maximum and minimum; OD, organ damage; PP, pulse pressure; PWV, pulse wave velocity; SBP, systolic BP; TC, total cholesterol; TRBPV, time rate of BP variation; VIM, variation independent of mean.

mean, and difference between maximum and minimum, independently of BP and other covariables.

For renal damage, Diaz et al identified ARV and TRBPV as independent determinants of renal function, positively correlated with glomerular filtration rate in a multivariate regression model that included age, body mass index, and mean 24-hour BP.<sup>51</sup> Later work by the same authors provided evidence that BPV was higher in subjects with impaired endothelial function and was associated with the vascular smooth muscle response to nitric oxide.<sup>52</sup> High ARV was also significantly associated with a greater vasodilatory response to nitroglycerin-mediated vasodilation<sup>53</sup> and elevated levels of high-sensitivity C-reactive protein,<sup>54</sup> independent of mean BP. High ARV was the strongest risk factor for endothelial dysfunction in a study that evaluated the relationship between various ambulatory BP parameters and flow-mediated dilatation in kidney transplant recipients.<sup>55</sup>

## Discussion

We conducted a systematic review to assess the predictive power of various BPV indexes on target organ damage and cardiovascular outcomes. Most studies found that ARV was a better estimator of 24-hour BPV than other measures of dispersion, including SD, CV, and wSD. Of the 19 assessed studies, 17 reported significant associations between high ARV and the presence and progression of subclinical organ damage,<sup>41–45,47–49,51–55</sup> as well as the incidence of hard end points, such as cardiovascular events.<sup>37–40</sup> For all these cases, ARV remained an independent predictor after adjustment for BP and other clinical factors. Moreover, in 11 of the 13 studies that included several BPV indexes, ARV was the best<sup>37,41,43,47,51,52</sup> or unique<sup>40,42,45,48,49</sup> significant predictor. In addition, our meta-analysis showed that increased ARV in systolic BP was associated with risk of all cardiovascular events. Only 2 cross-sectional studies did not find that high ARV was a significant risk factor. A study that computed ARV on the basis of a low minimum number of BP measurements (<20 daytime and 7 nighttime BP readings) found no association with preclinical organ damage.<sup>46</sup> Another study found no association between organ damage and 24-hour BPV, but did find a significant association with beat-to-beat recordings.<sup>50</sup>

Despite extensive evidence that 24-hour BPV, particularly ARV, provides superior predictive value than conventional BP indexes (SD, CV, and wSD), the regular use of 24-hour BPV in clinical practice remains problematic. Some studies have found that the contribution of ARV to stratification risk, although statistically significant, is low with for average BP levels. For example, the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome reports indicated that the incremental risk explained by adding ARV to models that included 24-hour ambulatory BP and other

covariables was only 0.1%.<sup>37,38</sup> However, these results might have been influenced by different methods of 24-hour ABPM used in the different cohort studies whose data were pooled in the analysis.<sup>6,57</sup>

On the other hand, heterogeneity in the metrics and protocols used in different studies is an overall problem in evaluating the predictive value of BPV.<sup>17,58</sup> Therefore, several methodological problems need to be addressed before BPV is routinely used in clinical practice. An important constraint is that the discontinuous nature of noninvasive ABPM devices might limit its accuracy in assessing rapid changes in BP.<sup>19,59</sup> Identification of an optimal measurement interval is key to the reliable estimation of the beat-by-beat oscillations that occur in seconds. Di Rienzo et al<sup>20</sup> demonstrated that quantification of SD using a time interval >15 minutes increases the potential error in estimating the true variance. However, short sampling intervals are rarely used in clinical settings, for practical reasons and because of the potential discomfort of patients.<sup>21</sup> The influence of the measurement interval gives the use of ARV an advantage over alternative approaches, such as TRBPV, which is potentially more sensitive to the sampling rate.<sup>22</sup>

Another methodological problem is that the minimum number of valid BP measurements needed to provide a reproducible and reliable assessment of BPV might not have been reached in all studies that use ARV. Mena et al concluded that 48 BP readings during a 24-hour period is sufficient to compute ARV without meaningful loss of prognostic information.<sup>39</sup> In fact, ARV might be less sensitive to missing readings and low sampling frequency than other BPV indexes. Eguchi et al<sup>60</sup> tested the reproducibility of ARV, SD, and wSD in hypertensive patients, before and after antihypertensive treatment. ARV exhibited the greatest reproducibility during both the observation and treatment periods. In agreement with those results, ARV was a significant predictor in 10 of the 11 studies with a minimum number of BP readings below the average lowest sampling rate.<sup>37,39,41,44,47,48,51–54</sup>

Although ARV has been shown to be a better predictor of risk than SD for most adverse outcomes,<sup>37,40–42,48,49</sup> studies to date have not estimated ARV using real-time monitoring, because no existing ABPM devices incorporate automatic quantification of ARV or other novel BPV indexes. The procedures for collection, computation, and storage of electronic BP recordings need to automatically provide accurate calculations of 24-hour BPV.

In conclusion, the current evidence suggests that the ARV index adds significant prognostic information to 24-hour ABPM, and is a useful approach for studying the clinical value of BPV. Moreover, technical features of ARV could resolve some methodological problems: ARV (1) is simple to compute, (2) is relatively insensitive to low sampling frequency, (3) is



not strongly influenced by cyclic components, (4) is sensitive to the sequential order of BP readings, and (5) provides insight into BP changes. However, even if ARV is accepted as the optimal index for reliable and reproducible evaluation of 24-hour BPV, methodological standardization is only an initial step for incorporating it in clinical practice. Further investigation is required to define potential diagnostic thresholds of abnormal BPV, to determine if reduction below those thresholds is associated with a decrease in target organ damage and/or risk of cardiovascular disease, to identify treatments that reduce BPV, and to clarify whether those therapeutic interventions provide additional prognostic benefit, independent of a reduction in mean BP.

## Acknowledgments

We acknowledge the South Texas Diabetes and Obesity Institute for support in preparation of this report.

## Sources of Funding

This work was supported by grants 1R01AG036469-01A1 and R03AG054186 from the National Institute on Aging and Fogarty International Center, and grants DSA/103.5/15/11115 and PFCE/2458/16 from Secretaria de Educación Pública, México.

## Disclosures

None.

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