Visit-to-Visit Variability in Blood Pressure and Kidney and Cardiovascular Outcomes in Patients With Type 2 Diabetes and Nephropathy: A Post Hoc Analysis From the RENAAL Study and the Irbesartan Diabetic Nephropathy Trial

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Background: Increased systolic blood pressure variability between outpatient visits is associated with increased incidence of cardiovascular end points. However, few studies have examined the association of visit-to-visit variability in systolic blood pressure with clinically relevant kidney disease outcomes. We analyzed the association of systolic blood pressure visit-to-visit variability with renal and cardiovascular morbidity and mortality among individuals with diabetes and nephropathy.

Study Design: Observational analysis of IDNT (Irbesartan Diabetic Nephropathy Trial) and the RENAAL (Reduction of End Points in Non–Insulin-Dependent Diabetes With the Angiotensin II Antagonist Losartan) Study.

Setting & Participants: 2,739 participants with type 2 diabetes and nephropathy with at least 1 year of blood pressure measurements available.

Predictors: Systolic blood pressure visit-to-visit variability was calculated from the SD of the systolic blood pressure from 4 visits occurring 3-12 months postrandomization.

Outcomes: The kidney disease outcome was defined as time to confirmed doubling of serum creatinine level, end-stage renal disease, or death; the cardiovascular outcome was defined as time to cardiovascular death, myocardial infarction, stroke, hospitalization for heart failure, or revascularization.

Results: Mean visit-to-visit variability in systolic blood pressure from 3 to 12 months postrandomization was 12.0 ± 6.8 (SD) mm Hg. Following this ascertainment period, there were 954 kidney disease and 542 cardiovascular events. Greater systolic blood pressure visit-to-visit variability was associated independently with increased risk of the composite kidney disease end point (HR per 1-SD increment, 1.08 [95% CI, 1.01-1.16]; \( P = 0.02 \)) and end-stage renal disease, but not with the cardiovascular outcome.

Limitations: Observational study with the potential for confounding.

Conclusions: In diabetic individuals with nephropathy, systolic blood pressure visit-to-visit variability is associated independently with hard kidney disease outcomes.


INDEX WORDS: Visit-to-visit variability in blood pressure; systolic blood pressure (SBP); diabetic kidney disease; kidney disease outcomes; Reduction of End Points in Non–Insulin-Dependent Diabetes With the Angiotensin II Antagonist Losartan (RENAAL).
albuminuria, a surrogate marker of kidney damage. These findings may be due in part to the impaired arteriolar autoregulation in the kidneys of such patients. This can lead to transmission of potentially harmful fluctuations in blood pressure to unprotected glomerular capillaries. However, the association of SBP visit-to-visit variability with progression of kidney disease, cardiovascular morbidity, and mortality is not established in patients with type 2 diabetes and nephropathy, a population for which blood pressure more strongly predicts such outcomes. Furthermore, a prospective association between increased SBP visit-to-visit variability and clinically significant kidney disease outcomes independent of important predictors, including baseline kidney function and albuminuria, has not been shown.

We therefore aimed to investigate whether SBP visit-to-visit variability was associated independently with renal and cardiovascular events and mortality in 2,739 individuals with nephropathy due to type 2 diabetes who were enrolled in either IDNT (Irbesartan Diabetic Nephropathy Trial) or the RENAAL (Reduction of End Points in Non—Insulin-Dependent Diabetes With the Angiotensin II Antagonist Losartan) Study.

METHODS

Study Design

IDNT and the RENAAL Study were 2 large, randomized, placebo-controlled, double-blind trials investigating the efficacy of an angiotensin receptor blocker (ARB; irbesartan in IDNT and losartan in RENAAL) in preventing hard kidney disease outcomes in patients with type 2 diabetes and nephropathy. In addition to irbesartan and placebo, IDNT included a calcium channel blocker (amlodipine) treatment arm. The rationale, study design, and outcomes of these trials have been published previously. Briefly, these trials were conducted from 1996 through 2000, with 87% of participants in IDNT and 65% in the RENAAL Study recruited from either Europe or North America. Patients were randomly assigned to placebo or active therapy with 75 mg of irbesartan, 2.5 mg/d of amlodipine (IDNT), or 50 mg/d of losartan (RENAAL) during two 4-week titration periods. Dosages of these drugs were increased to 300 mg/d, 10 mg/d, and 100 mg/d, respectively, in order to achieve blood pressure ≤ 135/85 mm Hg. Patients in the placebo groups were allowed to continue their antihypertensive medications with the exception of angiotensin-converting enzyme inhibitors and ARBs in both studies and calcium channel blockers in IDNT, which were discontinued prior to randomization. After the end of the 8-week titration period, dosages of other antihypertensive drugs were increased or additional antihypertensive agents were added to achieve the target blood pressure (except for angiotensin-converting enzyme inhibitors, ARBs, and, in IDNT, calcium channel blockers). Mean follow-up was 2.6 years for those enrolled in IDNT and 3.4 years for those in RENAAL.

Study Participants

A total of 3,228 adult patients with type 2 diabetes and nephropathy participated in the 2 studies (1,715 in IDNT and 1,513 in RENAAL). Inclusion criteria were similar, but there were minor differences. Eligible patients were aged 30-70 years and had type 2 diabetes, proteinuria (defined as protein excretion in a 24-hour urine sample > 900 mg in IDNT and > 500 mg in RENAAL), and serum creatinine level of 1.0-3.0 mg/dL in IDNT or 1.3-3.0 mg/dL in RENAAL (serum creatinine lower limits for males were 1.2 and 1.5 mg/dL, respectively). Patients with type 1 diabetes or known non-diabetic kidney disease were excluded. After randomization, patients were seen at 1 week, 4 weeks, 8 weeks, and 3 months and then subsequently at 3-month intervals.

For the purposes of performing this prospective cohort study, we included only the 2,739 individuals randomly assigned to the study with complete blood pressure readings from follow-up visits at 3, 6, 9, and 12 months postrandomization. In all outcomes analyses, we excluded individuals who had an event prior to the 12-month visit.

Blood Pressure and Other Measurements

In both trials, sitting SBP and diastolic blood pressure were measured at each study visit. Sitting blood pressure was measured on 3 occasions 1 minute apart after 5 minutes of rest in a seated position. Mean values for SBP and diastolic blood pressure from the 3 measurements were recorded for each visit. Serum creatinine and electrolytes also were measured at each study visit. The IDMS-traceable 4-variable MDRD (Modification of Diet in Renal Disease) Study equation was used to estimate glomerular filtration rate (GFR). Assessment of 24-hour urine albumin excretion was performed at the randomization visit and then every 3 months thereafter.

Each individual’s SBP visit-to-visit variability was calculated as the standard deviation (SD) of the mean SBP from 4 consecutive follow-up visits. In our primary analysis (N = 2,739), we calculated SBP visit-to-visit variability from the SBP measurements at the 3-, 6-, 9-, and 12-month postrandomization visits.

We selected these particular 4 visits to compute our primary SBP visit-to-visit variability exposure in order to avoid the use of blood pressure readings collected while antihypertensive medication dosages were being titrated, which could lead to misclassification of SBP visit-to-visit variability. The mean SBP visit-to-visit variability of the study population changed from baseline (ie, when it was computed from the first 4 consecutive visits at randomization, 1 week, 4 weeks, and 3 months) to beyond 3 months of follow-up (ie, when it was computed from the 4 consecutive visits at months 3, 6, 9, and 12), particularly among those receiving amlodipine (Fig S1, available as online supplementary material). However, from 3 months onward, the SBP visit-to-visit variability of each treatment group did not change significantly. In addition, using 4 visits to calculate SBP visit-to-visit variability proved a stable measurement for the study. As an example, the interclass correlation coefficient (ICC) between SBP visit-to-visit variability using the 4 blood pressure values from 3-12 months and that using the 4 blood pressures from 12-21 months was 0.42 (95% confidence interval [CI], 0.35-0.49). This compared favorably to the corresponding ICC when we used 5 visits to compute SBP visit-to-visit variability over similar time frames (ICC, 0.28; 95% CI, 0.21-0.37) and also to those reported in other studies (ICC, 0.34; 95% CI, 0.26-0.41).

Kidney Disease and Cardiovascular Outcomes

Consistent with the original end point definitions from these trials, we defined the primary kidney disease outcome in the present study as a composite of death, a confirmed doubling of serum creatinine level from baseline, or end-stage renal disease (ESRD). The latter was defined as the need for long-term dialysis therapy or kidney transplantation. An additional criterion for ESRD applied in IDNT was serum creatinine level ≥ 6 mg/dL (≥ 530 μmol/L). After the 3-month postrandomization visit, individuals returned for clinical assessment and measurement of serum creatinine every 3 months until completion of the study. As in the original trials, we...
analyzed a secondary cardiovascular outcome defined as the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for heart failure, or revascularization. All clinical end points were adjudicated by a blinded end point committee in the original trials using rigorous definitions applicable at the time.13,14

We performed a number of secondary analyses whereby individual components of the primary kidney disease outcome were analyzed separately. In addition, we separately analyzed cardiovascular death and stroke as individual outcomes.

**Statistical Analysis**

We first determined which baseline covariates were related to SBP visit-to-visit variability in univariable analysis. For covariates that had a continuous distribution, we performed univariable linear regression with SBP visit-to-visit variability as the independent continuous variable. The following continuous covariates were analyzed: age and mean values (from 3-12 months) for SBP, urinary albumin-creatinine ratio (which was log-transformed because of a skewed distribution), estimated GFR (eGFR), high-density lipoprotein cholesterol level, low-density lipoprotein cholesterol level, hemoglobin A1c level, and number of antihypertensive medications. Associations of SBP visit-to-visit variability with categorical covariates (including sex, race [white/black/Hispanic/Asian/other], smoking status [current/nonsmoker], treatment assignment [ARB, calcium channel blocker, or placebo], and trial [IDNT/RENAAL]) were analyzed with the Cochrane-Armitage test.

We then analyzed the associations of SBP visit-to-visit variability with the primary and secondary end points using Kaplan-Meier analysis and multivariable Cox proportional hazards regression. In all Cox proportional hazards analyses, we excluded individuals who had an event prior to the 12-month visit and used the 12-month postrandomization visit as time zero (ie, baseline). SBP visit-to-visit variability was examined as both a continuous (per 1-SD of SBP visit-to-visit variability) and a categorical variable (according to tertile of SBP visit-to-visit variability [low, moderate, or high]). The association of each end point with SBP visit-to-visit variability was analyzed separately for each treatment assignment (ARB, calcium channel blocker, or placebo) and with all treatment assignments combined. We also analyzed for interaction of treatment assignment on the association of SBP visit-to-visit variability with outcome. Multivariable Cox models included covariates that either were established risk factors for cardiovascular or kidney disease or were noted to have independent associations with SBP visit-to-visit variability from the analyses described. These included the following: age, sex, race, smoking status, study drug assignment (ARB, calcium channel blocker, or placebo), trial (IDNT/RENAAL), and mean (from 3-12 months) SBP, log-transformed albumin-creatinine ratio, and eGFR.

**RESULTS**

**Characteristics of the Study Population**

Mean SBP visit-to-visit variability in the placebo group was 12.4 ± 7.1 (SD) mm Hg (Table 1). That calculated in the ARB group was similar (12.2 ± 6.9 mm Hg), but was significantly lower among those receiving amlodipine (10.6 ± 6.0 mm Hg; P < 0.001). Change in SBP visit-to-visit variability was minimal among those receiving placebo and ARB therapy, but was markedly reduced among those receiving amlodipine (Fig S2). There was no substantial change in SBP visit-to-visit variability from 3 months onward.

The distribution of covariates across tertiles of SBP visit-to-visit variability (low, moderate, or high) in the group is listed in Table 1. Individuals in the RENAAL Study had higher SBP visit-to-visit variability than those in IDNT. Higher baseline, 12-month, and mean SBPs (calculated over the same 3- to 12-month period from which visit-to-visit variability was calculated) also were associated with higher visit-to-visit variability. Higher baseline and 3- to 12-month mean but not 12-month urine albumin-creatinine ratios also were associated with higher SBP visit-to-visit variability. Conversely, higher baseline, 12-month, and 3- to 12-month mean eGFRs were associated with lower SBP visit-to-visit variability. There was a significant association between a greater number of antihypertensive medications used at baseline and higher SBP visit-to-visit variability.

**Association of SBP Visit-to-Visit Variability With Kidney Disease and Cardiovascular Outcomes**

The survival curves for low, moderate, and high tertiles of SBP visit-to-visit variability for kidney disease end points (composite and individual) and all-cause mortality were significantly different (all log-rank P < 0.05); specifically, the cumulative incidence of events increased with increasing tertile (Fig 1). However, the cumulative incidence of cardiovascular mortality and of the composite of cardiovascular outcome was not different among tertiles. Results of multivariable Cox proportional hazards regression for the association of SBP visit-to-visit variability with all outcomes are shown in Table 2. After adjustment for potential confounders, every 1-SD increment in SBP visit-to-visit variability was associated significantly with increased risk of composite kidney disease end points (hazard ratio [HR], 1.08; 95% CI, 1.01-1.16; P = 0.02). Of the individual components of the composite kidney disease end points, ESRD (HR, 1.12; 95% CI, 1.02-1.22; P = 0.02) and all-cause mortality (HR, 1.16; 95% CI, 1.04-1.29; P = 0.007) showed a significant relation, whereas doubling of serum creatinine level was directionally similar but not significant (HR, 1.09; 95% CI, 1.00-1.19; P = 0.06). The HR for the association of higher SBP visit-to-visit variability and cardiovascular mortality was 1.15, but the result was not statistically significant (95% CI, 0.99-1.34; P = 0.07). There were no significant associations between SBP visit-to-visit variability and stroke or the composite of all cardiovascular events (Table 2). In all adjusted analyses, both the direction and magnitude of the association of SBP visit-to-visit variability with all outcomes were similar in each treatment assignment (ARB, calcium channel blocker, or placebo), with no significant interaction between study treatment assignment and SBP visit-to-visit variability with kidney disease or cardiovascular outcomes (Table 2).
DISCUSSION

In this large international cohort of individuals with type 2 diabetes and nephropathy, higher SBP visit-to-visit variability was associated prospectively and independently with increased risk of adverse kidney disease outcome even after controlling for SBP, eGFR, and urine albumin excretion. We found a similar association between elevated SBP visit-to-visit variability with overall mortality. We also observed that for individuals randomly assigned to ARB treatment, a decrease in SBP visit-to-visit variability upon initiation of therapy was associated with a decrease in risk of ESRD. Likewise, for individuals receiving amlodipine, a decrease in SBP visit-to-visit variability upon initiation of therapy was associated with decreased risk of cardiovascular mortality and stroke.

To our knowledge, this is the first study to document an association of SBP visit-to-visit variability with clinically important renal events independent of eGFR and urinary albumin excretion. In a prior study of African Americans with nondiabetic kidney disease, we showed that although such events were more common...
for those with higher SBP visit-to-visit variability, this relationship was confounded by the presence of proteinuria. Similarly, a retrospective study of older adults with chronic kidney disease (CKD) and hypertension (N = 374; median age, 79 years) found no association between SBP visit-to-visit variability and risk of ESRD (HR, 1.05; 95% CI, 0.94-1.17). A positive association of SBP visit-to-visit variability with ESRD or doubling of serum creatinine level was shown in a small retrospective study (N = 56), but the analysis was not adjusted for important confounders, such as urinary albumin excretion or eGFR. In a larger trial of individuals with type 2 diabetes (N = 8,811; <10% with macroalbuminuria), SBP visit-to-visit variability showed a variable association with the development of nephropathy; there was no association in a continuous analysis, but there was a trend toward worsening nephropathy in a categorical (by decile) analysis (P = 0.04). More importantly, these analyses did not adjust for baseline eGFR or urinary albumin excretion, both established risk factors for progression to kidney disease end points and previously shown to associate with SBP visit-to-visit variability, thereby failing to adjust for what likely are strong confounders of the association with kidney disease outcomes. Second, this larger analysis included the development of macroalbuminuria in the composite kidney disease end point, which has not been accepted as a clinically relevant kidney disease end point of equal importance to serum creatinine level doubling, ESRD, or death.

Although there have been several reports of the effects of antihypertensive medication class on SBP visit-to-visit variability, this is the first to report an association between change in SBP visit-to-visit variability measured upon initiation of a new antihypertensive treatment and subsequent kidney disease and cardiovascular outcomes. In this analysis, we found that a decrease in SBP visit-to-visit variability following initiating treatment with calcium channel blockers conferred a lower risk of cardiovascular death or stroke. Similarly, among individuals assigned to ARB treatment, a decrease in SBP visit-to-visit variability was associated with decreased risk of developing ESRD.

The mechanisms linking SBP visit-to-visit variability with adverse outcomes are unclear. This variability may simply be a marker of variation in an individual’s...
behavior (e.g., intermittent adherence to taking antihypertensive medication), a biomarker of cardiovascular damage, aortic stiffness due to fibrosis, or failure of autonomic blood pressure regulation. In cross-sectional analyses, for example, higher SBP visit-to-visit variability is associated with the following: poor adherence to antihypertensive medications; increased likelihood of smoking; greater degrees of albuminuria, higher renal resistive index, endothelial dysfunction, and increased carotid intima-media thickness; and decreased vascular elasticity, all biomarkers of cardiovascular damage. These numerous associations suggest that SBP visit-to-visit variability may represent an aggregate of high-risk behaviors and existing renal and cardiovascular damage. Alternatively, higher SBP visit-to-visit variability may be causally related to end-organ

**Table 2.** Hazard Ratios for Selected Outcomes With VVV as a Continuous Covariate

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Events</th>
<th>Adjusted 1$^a$</th>
<th>Adjusted 2$^b$</th>
<th>Adjusted 3$^c$</th>
<th>Adjusted 4$^d$</th>
<th>$P$ for Interaction$^e$</th>
</tr>
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<tbody>
<tr>
<td>Death/ESRD/Serum Creatinine Doubling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>954</td>
<td>1.22 (1.14-1.30)</td>
<td>1.13 (1.05-1.20)</td>
<td>1.08 (1.00-1.15)</td>
<td>1.08 (1.01-1.16)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>409</td>
<td>1.20 (1.09-1.32)</td>
<td>1.08 (0.98-1.19)</td>
<td>1.04 (0.94-1.15)</td>
<td>1.08 (0.98-1.19)</td>
<td></td>
</tr>
<tr>
<td>ARB</td>
<td>371</td>
<td>1.19 (1.07-1.32)</td>
<td>1.15 (1.03-1.29)</td>
<td>1.08 (0.96-1.21)</td>
<td>1.07 (0.95-1.20)</td>
<td></td>
</tr>
<tr>
<td>CCB</td>
<td>174</td>
<td>1.44 (1.21-1.72)</td>
<td>1.20 (1.01-1.44)</td>
<td>1.17 (0.97-1.40)</td>
<td>1.20 (0.98-1.46)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>366</td>
<td>1.22 (1.10-1.35)</td>
<td>1.16 (1.05-1.29)</td>
<td>1.17 (1.05-1.30)</td>
<td>1.16 (1.04-1.29)</td>
<td>0.5</td>
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<tr>
<td>Placebo</td>
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<td>1.17 (1.01-1.36)</td>
<td>1.10 (0.95-1.28)</td>
<td>1.11 (0.95-1.29)</td>
<td>1.11 (0.95-1.29)</td>
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<tr>
<td>ARB</td>
<td>162</td>
<td>1.26 (1.08-1.46)</td>
<td>1.22 (1.04-1.42)</td>
<td>1.20 (1.02-1.41)</td>
<td>1.20 (1.02-1.41)</td>
<td></td>
</tr>
<tr>
<td>CCB</td>
<td>48</td>
<td>1.18 (0.84-1.66)</td>
<td>1.13 (0.80-1.60)</td>
<td>1.27 (0.89-1.80)</td>
<td>1.20 (0.82-1.75)</td>
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</tr>
<tr>
<td>ESRD</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>608</td>
<td>1.25 (1.15-1.35)</td>
<td>1.14 (1.05-1.24)</td>
<td>1.07 (0.98-1.16)</td>
<td>1.09 (1.00-1.19)</td>
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<tr>
<td>Placebo</td>
<td>273</td>
<td>1.22 (1.09-1.37)</td>
<td>1.08 (0.96-1.21)</td>
<td>1.03 (0.91-1.17)</td>
<td>1.10 (0.98-1.24)</td>
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<tr>
<td>ARB</td>
<td>208</td>
<td>1.22 (1.07-1.39)</td>
<td>1.17 (1.02-1.35)</td>
<td>1.07 (0.92-1.24)</td>
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<tr>
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<td>1.48 (1.19-1.85)</td>
<td>1.22 (0.98-1.53)</td>
<td>1.15 (0.91-1.45)</td>
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<tr>
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<td>186</td>
<td>1.19 (1.03-1.38)</td>
<td>1.14 (0.99-1.33)</td>
<td>1.14 (0.98-1.33)</td>
<td>1.15 (0.99-1.34)</td>
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<td>76</td>
<td>1.21 (0.98-1.50)</td>
<td>1.14 (0.92-1.42)</td>
<td>1.14 (0.91-1.42)</td>
<td>1.14 (0.92-1.42)</td>
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<tr>
<td>ARB</td>
<td>90</td>
<td>1.13 (0.91-1.41)</td>
<td>1.09 (0.87-1.37)</td>
<td>1.07 (0.84-1.35)</td>
<td>1.09 (0.86-1.37)</td>
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<tr>
<td>CCB</td>
<td>20</td>
<td>1.37 (0.82-2.29)</td>
<td>1.43 (0.84-2.42)</td>
<td>1.59 (0.92-2.75)</td>
<td>1.63 (0.93-2.85)</td>
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<td>Cardiovascular Death</td>
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<tr>
<td>All</td>
<td>186</td>
<td>1.19 (1.03-1.38)</td>
<td>1.14 (0.99-1.33)</td>
<td>1.14 (0.98-1.33)</td>
<td>1.15 (0.99-1.34)</td>
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<tr>
<td>Placebo</td>
<td>76</td>
<td>1.21 (0.98-1.50)</td>
<td>1.14 (0.92-1.42)</td>
<td>1.14 (0.91-1.42)</td>
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<tr>
<td>ARB</td>
<td>90</td>
<td>1.13 (0.91-1.41)</td>
<td>1.09 (0.87-1.37)</td>
<td>1.07 (0.84-1.35)</td>
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<tr>
<td>CCB</td>
<td>20</td>
<td>1.37 (0.82-2.29)</td>
<td>1.43 (0.84-2.42)</td>
<td>1.59 (0.92-2.75)</td>
<td>1.63 (0.93-2.85)</td>
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<td>Composite Cardiovascular End Point</td>
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<tr>
<td>All</td>
<td>542</td>
<td>1.04 (0.94-1.13)</td>
<td>1.01 (0.93-1.11)</td>
<td>0.98 (0.89-1.08)</td>
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<tr>
<td>Placebo</td>
<td>245</td>
<td>0.99 (0.87-1.14)</td>
<td>0.97 (0.85-1.11)</td>
<td>0.94 (0.82-1.08)</td>
<td>0.95 (0.83-1.09)</td>
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<tr>
<td>ARB</td>
<td>217</td>
<td>1.09 (0.95-1.25)</td>
<td>1.07 (0.93-1.23)</td>
<td>1.04 (0.90-1.21)</td>
<td>1.05 (0.90-1.21)</td>
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<tr>
<td>CCB</td>
<td>80</td>
<td>1.02 (0.76-1.37)</td>
<td>1.02 (0.76-1.37)</td>
<td>0.94 (0.69-1.28)</td>
<td>0.95 (0.69-1.30)</td>
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<td>Stroke</td>
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<tr>
<td>All</td>
<td>N = 90</td>
<td>1.09 (0.87-1.35)</td>
<td>1.07 (0.86-1.33)</td>
<td>1.01 (0.80-1.27)</td>
<td>1.01 (0.80-1.27)</td>
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<tr>
<td>Placebo</td>
<td>N = 43</td>
<td>1.02 (0.75-1.39)</td>
<td>1.01 (0.74-1.38)</td>
<td>0.98 (0.71-1.36)</td>
<td>0.99 (0.72-1.36)</td>
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<tr>
<td>ARB</td>
<td>N = 36</td>
<td>1.12 (0.79-1.58)</td>
<td>1.08 (0.76-1.53)</td>
<td>1.02 (0.71-1.47)</td>
<td>1.02 (0.71-1.47)</td>
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<tr>
<td>CCB</td>
<td>N = 11</td>
<td>1.34 (0.62-2.91)</td>
<td>1.29 (0.59-2.80)</td>
<td>0.94 (0.39-2.23)</td>
<td>0.95 (0.40-2.24)</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Unless otherwise indicated, values are given as hazard ratio per 1 standard deviation of VVV (95% confidence interval).

Abbreviations: ARB, angiotensin receptor blocker; CCB, calcium channel blocker; ESRD, end-stage renal disease; VVV, visit-to-visit variability in systolic blood pressure.

$^a$Includes age, sex, smoker, trial, treatment assignment, and race.

$^b$Includes the covariates of Adjusted 1 in addition to mean glomerular filtration rate.

$^c$Includes the covariates of Adjusted 2 in addition to mean systolic blood pressure.

$^d$Includes the covariates of Adjusted 3 in addition to mean log-transformed urine albumin-creatinine ratio.

$^e$For an interaction with study treatment assignment.
damage potentially due to fluctuations in blood pressure exceeding local protective mechanisms of arterial and arteriolar autoregulation. In this cohort of type 2 diabetic individuals with nephropathy, it is interesting that SBP visit-to-visit variability was not associated with either cardiovascular mortality or a composite of cardiovascular events, although there was a nominal (but nonsignificant) association with cardiovascular mortality. This finding stands in contrast to a study of African Americans with hypertensive CKD, in which greater SBP visit-to-visit variability was associated strongly with increased cardiovascular mortality. This discrepancy likely reflects a difference in the association of SBP visit-to-visit variability with cardiovascular mortality, although it is not clear whether this is due to racial differences between cohorts, differences in the underlying disease (ie, diabetic vs nondiabetic; proteinuric vs nonproteinuric), or some other factor.

Because SBP visit-to-visit variability is defined as the change observed in an individual’s blood pressure measured at different times, it was important to assess whether this variability itself is a stable measurement when calculated over different periods for each individual. In this study, although population SBP visit-to-visit variability was found to be stable for each treatment group from 3 months onward, within individuals, it showed only moderate stability (ICC = 0.42 for SBP visit-to-visit variability measured during adjacent periods), suggesting that SBP visit-to-visit variability possibly changes as environmental or behavioral factors vary. In addition, SBP visit-to-visit variability is likely to reflect at least in part several stable factors. As evidence for an association between elevated SBP visit-to-visit variability and increased risk of cardiovascular and renal events accumulates, there is increased interest in assessing whether SBP visit-to-visit variability is a modifiable risk factor. Credence is lent to this hypothesis from the observation that individuals prescribed calcium channel blockers have less SBP visit-to-visit variability relative to individuals receiving β-blockers and also have lower stroke rates after adjusting for mean blood pressure and other risk factors. In an additional analysis, we calculated the change in SBP visit-to-visit variability for each individual from the period 0-3 months to 3-12 months and found that a decrease in this variability was associated with decreased risk of cardiac mortality and stroke in individuals taking amlodipine and decreased risk of ESRD in those taking ARBs. This suggests that antihypertensive medications may have benefit in reducing target-organ damage through increasing stability of blood pressure in addition to their purely blood pressure-lowering effects. In this study, SBP visit-to-visit variability was found to have similar associations with kidney disease and cardiovascular end points independent of treatment assignment. Therefore, although individuals assigned to calcium channel blocker treatment had overall lower mean SBP visit-to-visit variability than the other treatment assignments, within that treatment assignment, higher SBP visit-to-visit variability was associated with increased risk of kidney disease and cardiovascular outcomes, similar to those assigned to ARB or placebo treatment. The previous finding that individuals in IDNT assigned to calcium channel blocker treatment had increased risk of kidney disease outcome relative to those assigned to ARB treatment suggests that the benefits of ARB therapy are related to factors other than visit-to-visit variability of systemic blood pressure, which was lower in the calcium channel blocker group. This is consistent with the original report, which found that the benefits from ARB therapy were independent of achieved blood pressure during follow-up.

Our study has several limitations. First, although people with type 2 diabetes and nephropathy represent a large and important population for study, our findings do not necessarily extend to nondiabetic patients with CKD. Second, blood pressure control in trials generally is superior to that observed in general clinical practice. Although this might diminish the generalizability of our findings to some degree, the internal validity of our findings is increased by the attention given to participants in IDNT and RENAAL (thus limiting the effect of external factors on SBP visit-to-visit variability). Third, although IDNT and RENAAL were randomized trials, the present analysis was observational, and baseline covariates across SBP visit-to-visit variability tertiles had important differences, particularly in SBP and eGFR. Although our multivariable analyses included careful adjustment for these covariates, we cannot exclude the possibility of residual confounding from other important covariates that were not ascertained. Fourth, we did not have physiologic measurements of vascular or cardiac function, which limited the covariates that could be selected. However, we controlled for critically important risk factors for cardiovascular and renal events, and SBP visit-to-visit variability was an independent predictor after adjustment. Fifth, because this is an observational study, we cannot draw conclusions about the direction of the association between higher SBP visit-to-visit variability and increased risk of renal events. It is possible that individuals with more rapid decline in kidney function are at increased risk of fluid retention and therefore prone to blood pressure fluctuations, such that high SBP visit-to-visit variability may be a reflection of worsening kidney function. As a final note, we do not know that diabetes was the sole cause of nephropathy in this study. However, in a biopsy sub-study of 34 participants in IDNT, 94% had proven diabetic nephropathy, either with Kimmelsteil-Wilson...
nODULES (50%) or mesangial expansion and enlarged glomeruli (44%).31

Our study has several strengths. First, the large sample size (N = 2,739) with a high incidence rate of renal events (954 composite end point events) makes this the largest analysis to date to study the association of SBP visit-to-visit variability with kidney disease outcomes in individuals with CKD. Second, by selecting individuals with type 2 diabetes and advanced nephropathy, we have chosen not only a population at high risk for progression to renal and cardiovascular events, but also a population that is sensitive to blood pressure control and, by extension, at risk from increased blood pressure variability. Third, due to the prospective nature of the trials, individuals were followed up at regular prescribed intervals, allowing frequent measurement of blood pressure and other covariates; this permitted us to compute SBP visit-to-visit variability over a standardized period for each individual while simultaneously controlling for important potential confounders ascertained during the same standardized periods. Fourth, the end points in this study were adjudicated by an appointed end point committee with predefined criteria and therefore were highly reliable.

In conclusion, higher SBP visit-to-visit variability is associated with adverse kidney disease outcomes and overall mortality in patients with type 2 diabetes and nephropathy independent of antihypertensive medication and baseline kidney function. Further studies are required to elucidate whether modification of SBP visit-to-visit variability can reduce the progression of both kidney and cardiovascular disease.

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Contributions: Research idea and study design: CJM, HJLH, JPF, DdZ; data acquisition: H-HP, JPD, HJLH, and DdZ; data analysis/interpretation: CJM, HJLH; statistical analysis: CJM, HJLH; supervision or mentorship: JPF, DdZ. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. CJM takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained.

SUPPLEMENTARY MATERIAL

Figure S1: Measured SBP visit-to-visit variability over different periods for each study arm calculated using 4 visits.

Figure S2: Mean SBP during trials for each treatment arm.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2014.06.008) is available at www.ajkd.org

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