The Effect of Visit-to-Visit Variability in Blood Pressure on Stroke and Coronary Events in 5,213 Patients with Diabetes: Pooled Analyses of TNT, IDEAL, and CARDS Trials

Prakash Deedwania

University of California San Francisco, School of Medicine, Fresno, United States of America

On behalf of the TNT, IDEAL and CARDS Steering Committees
Presenter Disclosures

- Research grants from Pfizer Inc., consulting fees from Pfizer Inc. and AstraZeneca, and speaker’s honoraria from Pfizer Inc. and AstraZeneca
Background

- Visit-to-visit variability in systolic blood pressure (SBP):
  - Is reproducible and non-random\(^1\)
  - Is associated with increased all-cause mortality\(^2\)
  - Has been shown to predict cardiovascular risk independently of mean SBP in patients with hypertension and other cardiovascular risk factors\(^3,4\)
  - Is correlated with diabetic nephropathy and atherosclerosis and predicts all cause mortality in patients with type 2 diabetes\(^5,6\)

- We have shown previously that atorvastatin 80 mg versus 10 mg had no effect on BP\(^7\)

- It was of interest to analyse BP variability in this large cohort of diabetic patients from the TNT, IDEAL and CARDS trials

ASCOT: Visit-to-visit SBP Variability

<table>
<thead>
<tr>
<th>Standard deviation of SBP</th>
<th>Coefficient of variation of SBP</th>
<th>Variation independent of mean SBP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke Risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><img src="image1.png" alt="Graph" /></td>
<td><img src="image2.png" alt="Graph" /></td>
</tr>
<tr>
<td><strong>Coronary Risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><img src="image3.png" alt="Graph" /></td>
<td><img src="image4.png" alt="Graph" /></td>
</tr>
</tbody>
</table>

Objectives

- To determine the association between visit-to-visit variability in BP and the risk of cardiovascular events in the large cohorts of patients with diabetes from the TNT, IDEAL, and CARDS trials.

- To investigate whether visit-to-visit BP variability was associated with differences in clinical benefits observed with different statin therapies for patients with diabetes.
**Study Design: TNT Trial**

**Patient population**
- Coronary heart disease
- LDL-C: 130-250 mg/dL (3.4-6.5 mmol/L)
- Triglycerides: ≤600 mg/dL (≤6.8 mmol/L)
- 15% with type 2 diabetes

**Primary endpoint**
- Time to occurrence of first major CV event:
  - CHD death
  - Nonfatal, non-procedure-related MI
  - Resuscitated cardiac arrest
  - Fatal or nonfatal stroke

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**Screening and wash-out**
- n=18,469

**Open-label run-in**
- n=15,464

**Baseline**
- Atorvastatin 10 mg
- 1-8 weeks
- 8 weeks

**Double-blind period**
- n=10,001
- LDL-C: <130 mg/dL (<3.4 mmol/L)

- n=5006
  - Atorvastatin 10 mg
  - LDL-C target: 100 mg/dL (2.6 mmol/L)

- n=4995
  - Atorvastatin 80 mg
  - LDL-C target: 75 mg/dL (1.9 mmol/L)

Median follow-up = 4.9 years

Study Design: IDEAL Trial

Patient population
- History of recent or prior MI
- ≤80 years old
- Triglycerides: ≤600 mg/dL (≤6.8 mmol/L)
- 12% with type 2 diabetes

Primary endpoint
- Time to occurrence of a major coronary event (CHD death, nonfatal acute MI, resuscitated cardiac arrest)

Secondary endpoints
- Major CV events
- Any CHD event
- Any CV event
- Components of the composite endpoint
- All-cause mortality

Study Design: IDEAL Trial

Screening
n=9689

Randomization
n=8888

Baseline

No wash-out or run in

Open-label, blinded end point period
n=8888

Simvastatin 20 mg, titrated to 40 mg for TC >190mg/dL

n=4449

Atorvastatin 80 mg

n=4439

Median follow-up = 4.8 years

Study Design: CARDS Trial

**Patient population**
- Age: 40-75 years, no CVD
- LDL-C: ≤4.14 mmol/L (160 mg/dL)
- Triglycerides: ≤6.78 mmol/L (600 mg/dL)
- Type 2 diabetes and one of the following risk factors:
  - Hypertension, retinopathy, microalbuminuria or macroalbuminuria, current smoking

**Screening**
- n=4053

**Single-blind period**
- n=3249

**Baseline**
- Placebo

**Double-blind period**
- n=2838

- Atorvastatin 10 mg
- Placebo

**Primary endpoint**
- Time to first occurrence of acute coronary heart disease events, coronary revascularisation, or stroke

**Secondary endpoints**
- Effect of treatment on total mortality and effect of atorvastatin on any acute, hospital-verified cardiovascular endpoint

### Study Population

<table>
<thead>
<tr>
<th>Patients</th>
<th>Clinically evident CHD</th>
<th>History of MI</th>
<th>Type 2 diabetes and at least one other risk factor*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>4.9 years</td>
<td>4.8 years</td>
<td>3.9 years</td>
</tr>
<tr>
<td>Treatment</td>
<td>Atorvastatin 10 mg</td>
<td>Simvastatin 20-40 mg</td>
<td>Placebo Atorvastatin 10 mg</td>
</tr>
<tr>
<td>Visit-to-visit variability in BP, n†</td>
<td>711</td>
<td>512</td>
<td>1372</td>
</tr>
<tr>
<td></td>
<td>Atorvastatin 80 mg</td>
<td>Atorvastatin 80 mg</td>
<td>716</td>
</tr>
<tr>
<td></td>
<td></td>
<td>504</td>
<td>1398</td>
</tr>
</tbody>
</table>

*Hypertension, retinopathy, microalbuminuria or macroalbuminuria, current smoking
†Number of patients who had all post-baseline BP measurements
Coronary events were the composite of non-fatal MI, fatal CHD, non-fatal and fatal heart failure, and new onset angina in TNT and IDEAL; or MI (including silent MI), unstable angina, and acute coronary heart disease death in CARDS.

Visit-to-visit variability of BP was expressed in standard deviation (SD), coefficient of variation (CV), variability independent of mean (VIM), and average successive variability (ASV)\(^1\).

Cox regression model including treatment, mean SBP or DBP, and the corresponding visit-to-visit variability measurements of SBP or DBP, was employed to assess the risk of stroke and coronary events in relation to visit-to-visit variability in BP.

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**Methods**

**Statistics**

- **Visit-to-visit variability**:¹
  
  - $\text{VIM uncorrected} = (100 \times \text{SD}/\text{Mean}^{\beta})$, $\text{VIM} = \text{VIM uncorrected} \times (\text{mean of CV}) / (\text{mean of VIM uncorrected})$, where $\beta$ is the regression coefficient based on the natural logarithm of SD on the natural logarithm of mean.

  - $\text{ASV}$ is calculated as average absolute difference between successive values.

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Analysis Methods

**Coronary events**
- TNT and IDEAL: Nonfatal MI, fatal CHD, nonfatal and fatal heart failure, new onset angina
- CARDS: MI (including silent MI), unstable angina, and acute coronary heart disease death

**Visit-to-visit variability in BP**
- Standard deviation (SD)
- Coefficient of variation (CV)
- Variability independent of mean (VIM)
- Average successive variability (ASV)

**Cox regression model**
- Visit-to-visit variability in SBP and diastolic BP (DBP), as continuous variables or as deciles, on the risk of:
  - Stroke
  - Coronary events
## Results

### Visit-to-visit variability in SBP* and CV Risk

<table>
<thead>
<tr>
<th></th>
<th>Stroke</th>
<th>Coronary events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)†</td>
<td>P-value†</td>
</tr>
<tr>
<td><strong>TNT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rx + SD SBP</td>
<td>1.135 (0.919 – 1.402)</td>
<td>0.2388</td>
</tr>
<tr>
<td>Rx + CV SBP</td>
<td>1.129 (0.907 – 1.404)</td>
<td>0.2782</td>
</tr>
<tr>
<td>Rx + VIM SBP</td>
<td>1.123 (0.901 – 1.401)</td>
<td>0.3023</td>
</tr>
<tr>
<td>Rx + ASV SBP</td>
<td>1.143 (0.925 – 1.412)</td>
<td>0.2170</td>
</tr>
<tr>
<td><strong>IDEAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rx + SD SBP</td>
<td>1.423 (1.145 – 1.769)</td>
<td>0.0015</td>
</tr>
<tr>
<td>Rx + CV SBP</td>
<td>1.501 (1.202 – 1.873)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Rx + VIM SBP</td>
<td>1.519 (1.218 – 1.895)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Rx + ASV SBP</td>
<td>1.453 (1.194 – 1.768)</td>
<td>0.0002</td>
</tr>
<tr>
<td><strong>cards</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rx + SD SBP</td>
<td>1.254 (0.978 – 1.608)</td>
<td>0.0744</td>
</tr>
<tr>
<td>Rx + CV SBP</td>
<td>1.211 (0.938 – 1.565)</td>
<td>0.1417</td>
</tr>
<tr>
<td>Rx + VIM SBP</td>
<td>1.188 (0.918 – 1.538)</td>
<td>0.1897</td>
</tr>
<tr>
<td>Rx + ASV SBP</td>
<td>1.239 (0.973 – 1.578)</td>
<td>0.0828</td>
</tr>
</tbody>
</table>

*As continuous variables. †Hazard ratios (HRs) and P values are from the Cox regression model including treatment, mean SBP (as continuous variable), and the corresponding variability measurements of SBP (as continuous variable).
Results

Effect of visit-to-visit SBP* variability

**Stroke**
- SD SBP
- CV SBP
- VIM SBP
- ASV SBP

**Coronary events**

*As continuous variables
†P<0.05
Results

Visit-to-visit variability in SBP* and CV Risk

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**Stroke**

- Rx + SD SBP
- Rx + CV SBP
- Rx + VIM SBP
- Rx + ASV SBP
- Rx + mean SBP + SD SBP
- Rx + mean SBP + CV SBP
- Rx + mean SBP + VIM SBP
- Rx + mean SBP + ASV SBP

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**Coronary events**

- Rx + SD SBP
- Rx + CV SBP
- Rx + VIM SBP
- Rx + ASV SBP
- Rx + mean SBP + SD SBP
- Rx + mean SBP + CV SBP
- Rx + mean SBP + VIM SBP
- Rx + mean SBP + ASV SBP

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*As continuous variables
† P<0.001
‡ P<0.0001
Results

Effect of visit-to-visit DBP variability*

*As continuous variables
† P<0.05
‡ P<0.0001

SD DBP
CV DBP
VIM DBP
ASV DBP

Hazard ratio (95% CI)

TNT
IDEAL
CARDS

Hazard ratio (95% CI)
Results

Visit-to-visit variability in DBP* and CV Risk

Stroke

- Rx + SD DBP
- Rx + CV DBP
- Rx + VIM DBP
- Rx + ASV DBP
- Rx + mean DBP + SD DBP
- Rx + mean DBP + CV DBP
- Rx + mean DBP + VIM DBP
- Rx + mean DBP + ASV DBP

Coronary events

- Rx + mean DBP + ASV DBP

Hazard ratio (95% CI)

*As continuous variables
† P<0.05
‡ P<0.0001
Blood pressure measurements are nonlinear

SBP, DBP, and visit-to-visit variability in BP were also analyzed by deciles

- Risk of stroke was not significantly elevated with higher visit-to-visit variability in SBP or DBP

- Risk of coronary events was significantly increased in higher visit-to-visit variability in DBP only in the TNT cohort and with higher visit-to-visit variability in SBP only in the pooled cohort
## Results

**Treatment effect**

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>$\chi^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>0.67 (0.50 – 0.90)</td>
<td>7.2</td>
<td>0.0074</td>
</tr>
<tr>
<td>Coronary events</td>
<td>0.83 (0.70 – 0.98)</td>
<td>4.9</td>
<td>0.0268</td>
</tr>
</tbody>
</table>

n=5213
Conclusions

- In this cohort of high risk patients with diabetes, higher visit-to-visit variability in SBP is associated with significantly increased cardiovascular risk.

- The prognostic value of BP variability is consistent regardless of treatment effect and mean BP.

- The clinical benefit seen with intensive atorvastatin therapy in TNT and IDEAL, or atorvastatin versus placebo in CARDS, in reducing the risk of cardiovascular events is not mediated through reduction in BP variability.
Acknowledgments

TNT Steering Committee
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A Neil, Oxford, UK

Funding
The TNT and IDEAL studies were sponsored by Pfizer Inc. CARDS was funded by Diabetes UK, the UK Department of Health, Pfizer UK, and Pfizer Inc.
Back up
# Results

## Visit-to-visit variability in SBP* and CV Risk

<table>
<thead>
<tr>
<th></th>
<th><strong>Stroke</strong></th>
<th></th>
<th><strong>Coronary events</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P-value†</td>
<td>HR (95% CI)</td>
<td>P-value†</td>
</tr>
<tr>
<td>Rx + SD SBP</td>
<td>1.235 (1.096 – 1.391)</td>
<td>0.0005</td>
<td>1.185 (1.102 – 1.274)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rx + CV SBP</td>
<td>1.243 (1.099 – 1.405)</td>
<td>0.0005</td>
<td>1.213 (1.126 – 1.306)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rx + VIM SBP</td>
<td>1.243 (1.098 – 1.407)</td>
<td>0.0006</td>
<td>1.224 (1.136 – 1.318)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rx + ASV SBP</td>
<td>1.250 (1.116 – 1.399)</td>
<td>0.0001</td>
<td>1.181 (1.101 – 1.267)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rx + mean SBP + SD SBP</td>
<td>1.250 (1.098 – 1.423)</td>
<td>0.0007</td>
<td>1.223 (1.131 – 1.323)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rx + mean SBP + CV SBP</td>
<td>1.239 (1.095 – 1.403)</td>
<td>0.0007</td>
<td>1.220 (1.132 – 1.314)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rx + mean SBP + VIM SBP</td>
<td>1.241 (1.096 – 1.405)</td>
<td>0.0006</td>
<td>1.225 (1.137 – 1.319)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rx + mean SBP + ASV SBP</td>
<td>1.259 (1.118 – 1.419)</td>
<td>0.0002</td>
<td>1.207 (1.121 – 1.300)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*As continuous variables, data in this table are used to generate the forest plots in slide 11. †Hazard ratios (HRs) and P values are from the Cox regression model including treatment, mean SBP (as continuous variable), and the corresponding variability measurements of SBP (as continuous variable)
### Results

#### Visit-to-visit variability in DBP* and CV Risk

<table>
<thead>
<tr>
<th></th>
<th>Stroke</th>
<th></th>
<th></th>
<th>Coronary events</th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)†</td>
<td>P-value†</td>
<td></td>
<td>HR (95% CI)†</td>
<td>P-value†</td>
<td></td>
</tr>
<tr>
<td>Rx + SD SBP</td>
<td>1.175 (0.948 – 1.457)</td>
<td>0.1417</td>
<td></td>
<td>1.250 (1.109 – 1.409)</td>
<td>0.0003</td>
<td></td>
</tr>
<tr>
<td>Rx + CV SBP</td>
<td>1.227 (0.999 – 1.508)</td>
<td>0.0508</td>
<td></td>
<td>1.271 (1.134 – 1.425)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Rx + VIM SBP</td>
<td>1.166 (0.940 – 1.447)</td>
<td>0.1622</td>
<td></td>
<td>1.244 (1.104 – 1.403)</td>
<td>0.0004</td>
<td></td>
</tr>
<tr>
<td>Rx + ASV SBP</td>
<td>1.209 (0.986 – 1.483)</td>
<td>0.0682</td>
<td></td>
<td>1.367 (1.228 – 1.522)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Rx + SD SBP</td>
<td>1.229 (0.967 – 1.562)</td>
<td>0.0919</td>
<td></td>
<td>1.289 (1.128 – 1.473)</td>
<td>0.0002</td>
<td></td>
</tr>
<tr>
<td>Rx + CV SBP</td>
<td>1.311 (1.043 – 1.650)</td>
<td>0.0206</td>
<td></td>
<td>1.250 (1.190 – 1.312)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Rx + VIM SBP</td>
<td>1.239 (0.975 – 1.573)</td>
<td>0.0795</td>
<td></td>
<td>1.297 (1.135 – 1.482)</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Rx + ASV SBP</td>
<td>1.465 (1.182 – 1.816)</td>
<td>0.0005</td>
<td></td>
<td>1.234 (1.081 – 1.408)</td>
<td>0.0018</td>
<td></td>
</tr>
<tr>
<td>Rx + SD SBP</td>
<td>0.932 (0.705 – 1.233)</td>
<td>0.6234</td>
<td></td>
<td>1.041 (0.871 – 1.245)</td>
<td>0.6565</td>
<td></td>
</tr>
<tr>
<td>Rx + CV SBP</td>
<td>0.887 (0.667 – 1.180)</td>
<td>0.4098</td>
<td></td>
<td>1.040 (0.871 – 1.242)</td>
<td>0.6649</td>
<td></td>
</tr>
<tr>
<td>Rx + VIM SBP</td>
<td>0.938 (0.709 – 1.240)</td>
<td>0.6539</td>
<td></td>
<td>1.041 (0.871 – 1.245)</td>
<td>0.6574</td>
<td></td>
</tr>
<tr>
<td>Rx + ASV SBP</td>
<td>0.903 (0.677 – 1.205)</td>
<td>0.4882</td>
<td></td>
<td>1.107 (0.931 – 1.316)</td>
<td>0.2505</td>
<td></td>
</tr>
</tbody>
</table>

*As continuous variables, data in this table are used to generate the forest plots in slide 12. †Hazard ratios (HRs) and P values are from the Cox regression model including treatment, mean DBP (as continuous variable), and the corresponding variability measurements of DBP (as continuous variable)
## Results

### Visit-to-visit variability in DBP* and CV Risk

<table>
<thead>
<tr>
<th></th>
<th>Stroke HR (95% CI)†</th>
<th>P-value†</th>
<th>Coronary events HR (95% CI)†</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rx + SD DBP</td>
<td>1.123 (0.984 – 1.281)</td>
<td>0.0850</td>
<td>1.207 (1.120 – 1.301)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rx + CV DBP</td>
<td>1.161 (1.022 – 1.318)</td>
<td>0.0217</td>
<td>1.234 (1.149 – 1.325)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rx + VIM DBP</td>
<td>1.124 (0.986 – 1.282)</td>
<td>0.0806</td>
<td>1.206 (1.120 – 1.299)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rx + ASV DBP</td>
<td>1.203 (1.066 – 1.358)</td>
<td>0.0028</td>
<td>1.248 (1.164 – 1.337)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rx + mean DBP + SD DBP</td>
<td>1.119 (0.980 – 1.277)</td>
<td>0.0961</td>
<td>1.201 (1.114 – 1.295)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rx + mean DBP + CV DBP</td>
<td>1.131 (0.992 – 1.291)</td>
<td>0.0667</td>
<td>1.193 (1.107 – 1.285)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rx + mean DBP + VIM DBP</td>
<td>1.121 (0.983 – 1.279)</td>
<td>0.0876</td>
<td>1.202 (1.115 – 1.295)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rx + mean DBP + ASV DBP</td>
<td>1.195 (1.059 – 1.349)</td>
<td>0.0039</td>
<td>1.235 (1.153 – 1.324)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*As continuous variables, data in this table are used to generate the forest plots in slide 13. †Hazard ratios (HRs) and P values are from the Cox regression model including treatment, mean SBP (as continuous variable), and the corresponding variability measurements of SBP (as continuous variable).
# Results

*Visit-to-visit variability in SBP* and CV Risk

<table>
<thead>
<tr>
<th></th>
<th>Stroke</th>
<th></th>
<th>Coronaory events</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)†</td>
<td>P-value†</td>
<td>HR (95% CI)†</td>
<td>P-value†</td>
</tr>
<tr>
<td>Rx + SD SBP</td>
<td>1.767 (1.033 – 3.022)</td>
<td>0.0375</td>
<td>1.496 (1.088 – 2.058)</td>
<td>0.0133</td>
</tr>
<tr>
<td>Rx + CV SBP</td>
<td>1.704 (1.000 – 2.904)</td>
<td>0.0500</td>
<td>1.561 (1.143 – 2.132)</td>
<td>0.0051</td>
</tr>
<tr>
<td>Rx + VIM SBP</td>
<td>1.617 (0.954 – 2.741)</td>
<td>0.0746</td>
<td>1.630 (1.192 – 2.230)</td>
<td>0.0022</td>
</tr>
<tr>
<td>Rx + ASV SBP</td>
<td>1.641 (0.960 – 2.805)</td>
<td>0.0703</td>
<td>1.432 (1.033 – 1.987)</td>
<td>0.0313</td>
</tr>
<tr>
<td>Rx + mean SBP + SD SBP</td>
<td>1.797 (1.024 – 3.154)</td>
<td>0.0411</td>
<td>1.586 (1.134 – 2.219)</td>
<td>0.0071</td>
</tr>
<tr>
<td>Rx + mean SBP + CV SBP</td>
<td>1.665 (0.974 – 2.849)</td>
<td>0.0625</td>
<td>1.543 (1.127 – 2.112)</td>
<td>0.0067</td>
</tr>
<tr>
<td>Rx + mean SBP + VIM SBP</td>
<td>1.587 (0.936 – 2.692)</td>
<td>0.0867</td>
<td>1.598 (1.167 – 2.186)</td>
<td>0.0034</td>
</tr>
<tr>
<td>Rx + mean SBP + ASV SBP</td>
<td>1.686 (0.966 – 2.940)</td>
<td>0.0659</td>
<td>1.482 (1.056 – 2.080)</td>
<td>0.0230</td>
</tr>
</tbody>
</table>

*As deciles; †HRs and P-values are from the Cox regression model for top decile versus bottom decile of variability in SBP*
## Results

### Visit-to-visit variability in DBP* and CV Risk

<table>
<thead>
<tr>
<th></th>
<th>Stroke</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)†</td>
<td>P-value†</td>
<td>HR (95% CI)†</td>
<td>P-value†</td>
</tr>
<tr>
<td><strong>Rx + SD DBP</strong></td>
<td>1.233 (0.727 – 2.092)</td>
<td>0.4367</td>
<td>1.830 (1.310 – 2.556)</td>
<td>0.0004</td>
</tr>
<tr>
<td><strong>Rx + CV DBP</strong></td>
<td>1.299 (0.768 – 2.196)</td>
<td>0.3293</td>
<td>1.766 (1.257 – 2.483)</td>
<td>0.0011</td>
</tr>
<tr>
<td><strong>Rx + VIM DBP</strong></td>
<td>1.134 (0.659 – 1.953)</td>
<td>0.6488</td>
<td>1.653 (1.187 – 2.300)</td>
<td>0.0029</td>
</tr>
<tr>
<td><strong>Rx + ASV DBP</strong></td>
<td>1.684 (0.947 – 2.994)</td>
<td>0.0762</td>
<td>1.359 (0.982 – 1.880)</td>
<td>0.0642</td>
</tr>
<tr>
<td><strong>Rx + mean DBP + SD DBP</strong></td>
<td>1.205 (0.704 – 2.061)</td>
<td>0.4960</td>
<td>1.702 (1.213 – 2.386)</td>
<td>0.0021</td>
</tr>
<tr>
<td><strong>Rx + mean DBP + CV DBP</strong></td>
<td>1.224 (0.707 – 2.118)</td>
<td>0.4709</td>
<td>1.514 (1.064 – 2.153)</td>
<td>0.0210</td>
</tr>
<tr>
<td><strong>Rx + mean DBP + VIM DBP</strong></td>
<td>1.130 (0.652 – 1.959)</td>
<td>0.6630</td>
<td>1.546 (1.107 – 2.159)</td>
<td>0.0106</td>
</tr>
<tr>
<td><strong>Rx + mean DBP + ASV DBP</strong></td>
<td>1.667 (0.932 – 2.982)</td>
<td>0.0850</td>
<td>1.284 (0.925 – 1.781)</td>
<td>0.1352</td>
</tr>
</tbody>
</table>

*As deciles; †HRs and P-values are from the Cox regression model for top decile versus bottom decile of variability in DBP
# Results

*Treatment effect adjusted for visit-to-visit variability in BP*

<table>
<thead>
<tr>
<th></th>
<th>Stroke HR (95% CI)†</th>
<th>Stroke P-value†</th>
<th>Coronary events HR (95% CI)†</th>
<th>Coronary events P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rx</td>
<td>0.672 (0.502 – 0.899)</td>
<td>0.0074</td>
<td>0.827 (0.699 – 0.978)</td>
<td>0.0268</td>
</tr>
<tr>
<td>Rx + SD SBP</td>
<td>0.682 (0.510 – 0.913)</td>
<td>0.0101</td>
<td>0.836 (0.706 – 0.989)</td>
<td>0.0372</td>
</tr>
<tr>
<td>Rx + CV SBP</td>
<td>0.683 (0.510 – 0.914)</td>
<td>0.0103</td>
<td>0.838 (0.708 – 0.991)</td>
<td>0.0392</td>
</tr>
<tr>
<td>Rx + VIM SBP</td>
<td>0.683 (0.510 – 0.914)</td>
<td>0.0103</td>
<td>0.838 (0.708 – 0.992)</td>
<td>0.0400</td>
</tr>
<tr>
<td>Rx + ASV SBP</td>
<td>0.681 (0.509 – 0.911)</td>
<td>0.0098</td>
<td>0.833 (0.704 – 0.986)</td>
<td>0.0337</td>
</tr>
<tr>
<td>Rx + mean DBP + SD SBP</td>
<td>0.682 (0.510 – 0.913)</td>
<td>0.0102</td>
<td>0.837 (0.707 – 0.990)</td>
<td>0.0382</td>
</tr>
<tr>
<td>Rx + mean DBP + CV SBP</td>
<td>0.683 (0.510 – 0.914)</td>
<td>0.0103</td>
<td>0.837 (0.708 – 0.991)</td>
<td>0.0390</td>
</tr>
<tr>
<td>Rx + mean DBP + VIM SBP</td>
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<td>0.0398</td>
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<tr>
<td>Rx + mean DBP + ASV SBP</td>
<td>0.681 (0.509 – 0.911)</td>
<td>0.0098</td>
<td>0.833 (0.704 – 0.986)</td>
<td>0.0333</td>
</tr>
<tr>
<td>Rx + SD DBP</td>
<td>0.675 (0.505 – 0.904)</td>
<td>0.0083</td>
<td>0.836 (0.706 – 0.989)</td>
<td>0.0367</td>
</tr>
<tr>
<td>Rx + CV DBP</td>
<td>0.675 (0.504 – 0.903)</td>
<td>0.0081</td>
<td>0.833 (0.704 – 0.985)</td>
<td>0.0330</td>
</tr>
<tr>
<td>Rx + VIM DBP</td>
<td>0.676 (0.505 – 0.904)</td>
<td>0.0083</td>
<td>0.836 (0.706 – 0.989)</td>
<td>0.0370</td>
</tr>
<tr>
<td>Rx + ASV DBP</td>
<td>0.678 (0.505 – 0.907)</td>
<td>0.0089</td>
<td>0.835 (0.705 – 0.988)</td>
<td>0.0354</td>
</tr>
<tr>
<td>Rx + mean DBP + SD DBP</td>
<td>0.672 (0.502 – 0.899)</td>
<td>0.0075</td>
<td>0.828 (0.700 – 0.980)</td>
<td>0.0279</td>
</tr>
<tr>
<td>Rx + mean DBP + CV DBP</td>
<td>0.672 (0.502 – 0.899)</td>
<td>0.0075</td>
<td>0.826 (0.698 – 0.978)</td>
<td>0.0264</td>
</tr>
<tr>
<td>Rx + mean DBP + VIM DBP</td>
<td>0.672 (0.502 – 0.900)</td>
<td>0.0076</td>
<td>0.828 (0.700 – 0.980)</td>
<td>0.0282</td>
</tr>
<tr>
<td>Rx + mean DBP + ASV DBP</td>
<td>0.674 (0.504 – 0.902)</td>
<td>0.0080</td>
<td>0.827 (0.699 – 0.979)</td>
<td>0.0269</td>
</tr>
</tbody>
</table>

*As continuous variables. †Hazard ratios (HRs) and P values are from the Cox regression model including treatment, mean BP, and the corresponding variability measurements of BP*