Effect of Antihypertensive Agents on Blood Pressure Variability

The Natrilix SR Versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients (X-CELLENT) Study

Yi Zhang, Davide Agnoletti, Michel E. Safar, Jacques Blacher

See Editorial Commentary, pp 133–135

Abstract—To investigate the effect of different antihypertensive agents on blood pressure (BP) variability (BPV) and the underlying mechanism, we analyzed the ambulatory BP monitoring data of 577 patients before and after 3-month antihypertensive treatment, in the Natrilix SR Versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients (X-CELLENT) Study, a multicenter, multinational, randomized, double-blind, placebo-controlled study with 4 parallel treatment arms (placebo, candesartan, indapamide sustained release, and amlodipine). Within-subject mean and SD of 24-hour BP, weighted by time interval between consecutive readings, were calculated in 3 time frames (daytime, nighttime, and 24 hours) to evaluate BP and BPV. The mean 24-hour heart rate (HR) and HR variability were calculated with the same algorithms. We found that the 3 antihypertensive drugs had a similar BP-lowering effect ($P<0.001$ for all), but amlodipine ($P<0.007$) and indapamide sustained release ($P<0.04$) were the only agents associated with a significantly decreased BPV after 3-month treatment. On the other hand, the major determinants of BPV at baseline were age, mean BP, and the corresponding HR variability. However, the reduction in BPV by amlodipine was significantly associated with the reduction in BP ($P<0.006$) and the reduction in HR variability ($P<0.02$), whereas the corresponding reduction by indapamide sustained release was only associated with the reduction in HR variability at night ($P=0.004$). In summary, 3-month amlodipine or indapamide sustained release treatment was associated with a significant reduction in BPV, and the mechanism of those reductions was possibly attributable to lowering BP or ameliorating the autonomic nervous system regulation or both. The combination of the 2 agents might help to optimize such properties. (Hypertension. 2011;58:155-160.)

Key Words: ambulatory blood pressure monitoring ■ calcium channel blocker ■ diuretics ■ blood pressure variability ■ heart rate variability

For many decades, the main goal of antihypertensive treatment was to lower blood pressure (BP) to a defined level. Recently, several investigators have shown that BP variability (BPV) is another critical cardiovascular risk factor, which should also be emphasized in the treatment of hypertension. Mancia et al1 were the first to report a close association of BPV, assessed by 24-hour ambulatory BP monitoring (ABPM), with target-organ damage in hypertensive patients. Carotid artery damage1 and increased left ventricular mass index2 were, therefore, investigated in the first instance. However, the predictive value of BPV concerning cardiovascular and all-cause mortality has long been a matter of debate.3–9 More recently, nighttime BPV was considered to be a more pronounced risk factor than daytime BPV.10,11 Finally, Rothwell12 showed that visit-to-visit BPV was an independent and strong predictor of cardiovascular events, such as stroke and coronary heart disease, and calcium channel blockers and nonloop diuretics were the most effective antihypertensive agents in reducing BPV and in preventing stroke.13

However, the unique effect of these agents in terms of BPV reduction is still unproved in the setting of randomized, double-blind, placebo-controlled study. Similar observations can be made regarding other antihypertensive agents as diuretics, β-blocking agents, and blockers of the renin-angiotensin-aldosterone system. Finally, the determinants of BPV remain unclear, and the underlying mechanism of BPV...
reduction has never been elucidated precisely in subjects with hypertension.

We analyzed the ABPM data of 577 patients before and after 3-month antihypertensive treatment, in a multicenter, multinational, randomized, double-blind, placebo-controlled study with 4 parallel treatment arms (the Natrilix SR Versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients [X-CELLENT] Study), to investigate the effect of different antihypertensive agents on BPV and the underlying mechanism.

Methods

Study Design

The X-CELLENT Study was conducted in 2370 outpatients (aged between 40 and 80 years) with essential hypertension. The inclusion criteria included 150 mm Hg systolic BP or 90 mm Hg diastolic BP, as calculated by the formula mentioned in Methods; SR, sustained release.

Diastolic blood pressure, mm Hg 85.4 ± 12.5 140.9 ± 140.8 ± 12.1 141.8 ± 13.2 0.90

Characteristics of Subjects at Baseline

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (n=141)</th>
<th>Candesartan (n=141)</th>
<th>Indapamide SR (n=146)</th>
<th>Amlodipine (n=149)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58.9 ± 10.1</td>
<td>59.0 ± 10.2</td>
<td>58.6 ± 10.2</td>
<td>59.4 ± 10.1</td>
<td>0.93</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>69 (48.9)</td>
<td>57 (40.4)</td>
<td>75 (51.4)</td>
<td>84 (56.4)</td>
<td>0.06</td>
</tr>
<tr>
<td>Body mass index, g/m²</td>
<td>26.8 ± 3.0</td>
<td>27.1 ± 3.1</td>
<td>27.1 ± 3.1</td>
<td>26.8 ± 3.2</td>
<td>0.67</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>18 (12.8)</td>
<td>20 (14.2)</td>
<td>24 (16.4)</td>
<td>25 (16.8)</td>
<td>0.37</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>141.5 ± 12.5</td>
<td>140.9 ± 13.3</td>
<td>140.8 ± 12.1</td>
<td>141.8 ± 13.2</td>
<td>0.90</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>85.4 ± 9.1</td>
<td>85.1 ± 9.6</td>
<td>85.1 ± 8.6</td>
<td>86.0 ± 9.3</td>
<td>0.81</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>75.8 ± 10.2</td>
<td>75.2 ± 9.2</td>
<td>75.0 ± 9.5</td>
<td>74.7 ± 10.4</td>
<td>0.83</td>
</tr>
<tr>
<td>Previous antihypertensive therapy, n (%)</td>
<td>82 (58.2)</td>
<td>82 (58.2)</td>
<td>77 (52.7)</td>
<td>86 (57.7)</td>
<td>0.74</td>
</tr>
<tr>
<td>Daytime systolic blood pressure SD, mm Hg</td>
<td>13.0 ± 3.7</td>
<td>12.8 ± 3.2</td>
<td>12.9 ± 3.2</td>
<td>12.7 ± 3.1</td>
<td>0.86</td>
</tr>
<tr>
<td>Nighttime systolic blood pressure SD, mm Hg</td>
<td>11.0 ± 3.3</td>
<td>10.9 ± 2.8</td>
<td>10.9 ± 3.3</td>
<td>10.9 ± 3.3</td>
<td>0.99</td>
</tr>
<tr>
<td>Daily systolic blood pressure SD, mm Hg</td>
<td>12.3 ± 3.2</td>
<td>12.0 ± 2.5</td>
<td>12.2 ± 2.7</td>
<td>12.1 ± 2.6</td>
<td>0.84</td>
</tr>
<tr>
<td>ARV, mm Hg</td>
<td>9.3 ± 1.8</td>
<td>9.4 ± 1.7</td>
<td>9.5 ± 1.9</td>
<td>9.5 ± 1.8</td>
<td>0.61</td>
</tr>
<tr>
<td>Plasma glucose, mmol/L</td>
<td>5.26 ± 0.68</td>
<td>5.12 ± 0.73</td>
<td>5.27 ± 1.06</td>
<td>5.25 ± 0.67</td>
<td>0.34</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.76 ± 1.03</td>
<td>5.72 ± 0.98</td>
<td>5.74 ± 0.94</td>
<td>5.80 ± 0.99</td>
<td>0.92</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol, mmol/L</td>
<td>1.56 ± 0.41</td>
<td>1.52 ± 0.35</td>
<td>1.56 ± 0.40</td>
<td>1.53 ± 0.33</td>
<td>0.78</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol, mmol/L</td>
<td>3.51 ± 0.93</td>
<td>3.54 ± 0.85</td>
<td>3.49 ± 0.88</td>
<td>3.60 ± 0.86</td>
<td>0.74</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.52 ± 1.01</td>
<td>1.46 ± 0.83</td>
<td>1.48 ± 0.83</td>
<td>1.49 ± 0.92</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Values are mean ± SD or No. with percentage in parenthesis. ARV indicates the read-to-read average real variability, which is calculated by the formula mentioned in Methods; SR, sustained release.

Calculation of BP and Heart Rate Variability

To minimize the effects of recording errors during the 24-hour ABPM, we used the within-subject mean and SD, weighted for the time interval between consecutive validated readings, to evaluate BP and BPV. Considering nighttime dipping, mean and SD were calculated for the times awake and asleep, as daytime mean, daytime SD, nighttime mean, and nighttime SD. The overall mean and SD, as daily mean and daily SD, were assessed using the following 2 formulas: (1) daily mean = (daytime mean × AT + nighttime mean × ST)/(AT + ST) and (2) daily SD = (daytime SD × AT + nighttime SD × ST)/(AT + ST), where AT and ST stand for awake time and sleeping time in hours.

Another parameter, read-to-read average real variability (ARV), recently proposed by other investigators, was also used to evaluate BPV, as calculated by the following formula:

\[ \text{ARV} = \frac{1}{n} \sum_{k=1}^{n} w_k |B_{k-1} - B_k| \]

where \( k \) ranges from 1 to N, \( w \) is the time interval between \( B_{k-1} \) and \( B_k \), and \( n \) is the number of BP readings in 24 hours.

The mean value of 24-hour heart rate (HR) and HR variability (HRV) were assessed with the same algorithms as the BP.

Statistical Analysis

Quantitative and qualitative parameters were presented as mean ± SD and absolute number with percentage in parentheses, respectively. We used the ANOVA to compare the mean and variability of BP, as well as biochemical variables, between subjects with different antihypertensive treatments at baseline, and applied the Student's \( t \) test
and the generalized linear regression to compared BPV between treatment and placebo groups, before and after adjustment for corresponding BP reduction. Multivariate linear regression analysis was used to investigate determinants of BPV and the reduction in BPV by indapamide SR and amlodipine, separately. Statistical analysis was performed using SAS software, version 9.1 (SAS Institute, Cary, NC). P<0.05 was considered as statistically significant.

**Results**

Table 1 shows the characteristics of subjects at baseline according to randomized antihypertensive therapy. There was no significant difference between groups. After 3-month antihypertensive treatment, 496 subjects underwent a second ABPM, and there was no significant difference in characteristics between subjects with (n=497) or without the repeat ABPM (n=82).

In Table 2, compared with placebo, all 3 of the antihypertensive agents significantly decreased systolic BP in the 3 time frames, daytime, nighttime, and 24 hours ($P<0.001$ for all), whereas amlodipine and indapamide SR were the only antihypertensive agents to significantly decrease systolic BPV. Specifically, amlodipine significantly decreased systolic BPV in the 3 time frames ($P<0.008$ for all), and indapamide SR significantly decreased systolic BPV in the daytime ($P=0.03$) and 24 hours ($P=0.03$). However, candesartan did not reduce systolic BPV in any time frame. The similar findings are presented in the Figure. In addition, although no significant difference in systolic BPV was observed in the 24-hour read-to-read ARV mode after 3-month different antihypertensive treatments ($P=0.08$), the reduction in ARV by amlodipine also reached statistical significance ($P=0.007$). Furthermore, even after adjustment for the corresponding mean BP reduction, the present findings remained unaltered, except that the reduction in daily BPV by indapamide lost its previous significance ($P=0.06$).

When subjects at baseline were investigated, the determinants of systolic BPV were studied in different modes, such as Table 2. Changes in Systolic Blood Pressure and Its Variability by Treatment Group vs Placebo After 3-mo Treatment

<table>
<thead>
<tr>
<th>Variables</th>
<th>Placebo (n=120)</th>
<th>Candesartan (n=120)</th>
<th>Indapamide SR (n=133)</th>
<th>Amlodipine (n=123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime mean</td>
<td>146.6±13.8</td>
<td>135.7±14.0</td>
<td>137.4±12.8</td>
<td>137.3±10.3</td>
</tr>
<tr>
<td>Change vs placebo</td>
<td>10.9 (−14.5, −7.4)</td>
<td>9.2 (−12.5, −5.9)</td>
<td>9.3 (−12.4, −6.2)</td>
<td></td>
</tr>
<tr>
<td>Nighttime mean</td>
<td>131.2±14.8</td>
<td>120.2±16.7</td>
<td>120.9±12.8</td>
<td>120.8±10.5</td>
</tr>
<tr>
<td>Change vs placebo</td>
<td>11.0 (−15.2, −6.8)</td>
<td>10.3 (−13.8, −6.8)</td>
<td>10.5 (−13.8, −7.2)</td>
<td></td>
</tr>
<tr>
<td>Daily mean</td>
<td>141.9±13.5</td>
<td>130.6±13.7</td>
<td>132.0±11.7</td>
<td>131.9±9.3</td>
</tr>
<tr>
<td>Change vs placebo</td>
<td>11.2 (−14.8, −7.6)</td>
<td>9.8 (−13.1, −6.6)</td>
<td>9.9 (−12.9, −6.9)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure variability, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime SD</td>
<td>13.2±3.4</td>
<td>12.6±3.2</td>
<td>12.3±3.0</td>
<td>12.0±3.1</td>
</tr>
<tr>
<td>Change vs placebo</td>
<td>−0.6 (−1.4, 0.3)</td>
<td>−0.9 (−1.7, −0.1)</td>
<td>−1.1 (−1.9, −0.3)</td>
<td></td>
</tr>
<tr>
<td>$P$ after adjustment</td>
<td></td>
<td>0.23</td>
<td>0.04</td>
<td>0.009</td>
</tr>
<tr>
<td>Nighttime SD</td>
<td>11.4±3.2</td>
<td>11.4±3.3</td>
<td>10.7±3.3</td>
<td>10.2±3.1</td>
</tr>
<tr>
<td>Change vs placebo</td>
<td>−0.3 (−0.8, 0.9)</td>
<td>−0.7 (−1.5, 0.2)</td>
<td>−1.2 (−2.0, −0.4)</td>
<td></td>
</tr>
<tr>
<td>$P$ after adjustment</td>
<td></td>
<td>0.92</td>
<td>0.17</td>
<td>0.006</td>
</tr>
<tr>
<td>Daily SD</td>
<td>12.4±2.7</td>
<td>12.2±2.7</td>
<td>11.7±2.5</td>
<td>11.5±2.6</td>
</tr>
<tr>
<td>Change vs placebo</td>
<td>−0.3 (−1.0, 0.4)</td>
<td>−0.7 (−1.4, −0.1)</td>
<td>−1.0 (−1.6, −0.3)</td>
<td></td>
</tr>
<tr>
<td>$P$ after adjustment</td>
<td></td>
<td>0.58</td>
<td>0.06</td>
<td>0.008</td>
</tr>
<tr>
<td>ARV</td>
<td>9.5±1.7</td>
<td>9.3±1.9</td>
<td>9.3±1.9</td>
<td>8.9±1.7</td>
</tr>
<tr>
<td>Change vs placebo</td>
<td>−0.2 (−0.7, 0.3)</td>
<td>−0.3 (−0.7, 0.2)</td>
<td>−0.6 (−1.0, −0.2)</td>
<td></td>
</tr>
<tr>
<td>$P$ after adjustment</td>
<td></td>
<td>0.42</td>
<td>0.40</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Values are mean±SD. Daytime mean and SD=time-weighted mean and SD of 24-h systolic blood pressure readings during awake time; nighttime mean and SD=time-weighted mean and SD of 24-h systolic blood pressure readings during sleeping time; daily mean and SD=(daytime mean [SD]×awake time+nighttime mean [SD]×sleeping time)/(awake time+sleeping time). ARV indicates the read-to-read average real variability, which is calculated by the formula mentioned in the Methods. Change vs placebo indicates value from treatment groups minus that from placebo, and mean and 95% CI are presented. $P$ after adjustment indicates $P$ after adjustment for the corresponding mean blood pressure reduction.
as in the daytime, nighttime, 24-hour, and 24-hour read-to-read ARV modes (Table 3). Age, mean systolic BP, and HRV evaluated by the corresponding mode were major determinants of systolic BPV.

As shown in Table 4, the reduction in systolic BPV by amlodipine in different time frames and modes was largely attributable to the reduction in mean systolic BP ($P<0.006$) and the reduction in the corresponding HRV ($P<0.02$), whereas the corresponding reduction by indapamide SR was only attributed to the reduction in HRV at night ($P=0.004$) and mean BP ($P=0.003$).

### Discussion

In the present study, the 3 main findings were as follows: (1) although no effect on BPV was noted for candesartan, 3-month amlodipine treatment decreased systolic BPV in the daytime, nighttime, and 24 hours, and 3-month indapamide SR therapy reduced systolic BPV in the daytime and 24 hours; (2) the major determinants of baseline systolic BPV were age, mean systolic BP, and HRV; and (3) the reduction in systolic BPV by amlodipine was attributable to the reduction in mean systolic BP and in HRV, whereas the cause of the corresponding reduction by indapamide SR was largely unknown.

In the literature, several investigators have shown that calcium channel blockers significantly reduce BPV, as assessed by the SD of 24-hour BP, and which is in line with the present study. However, some of these investigators also reported that, when BPV is assessed by coefficient of variability, calculated as SD divided by mean BP, the previous significant reduction is absent. In this respect, we preferred to assess BPV by using SD, for 2 main reasons. First, from a statistical point of view, it is not valid to evaluate the reduction in BPV independent of BP level with a robust division as using coefficient of variability, because some statistical efficacy would be lost. For instance, in the present study, we did not find a significant decrease of BPV in terms of coefficient of variability, but the statistical significance was preserved when we compared the after-treatment BPV between different treatment groups, after adjustment for the mean value of BP (data not shown). Second, from a prognostic viewpoint, a close association of target-organ damage, cardiovascular events, and mortality with SD of 24-hour BP has frequently been reported in various population-based studies, but the prognostic value concerning the coefficient of variability of BP is very limited in literature. Accordingly, we assessed the BPV by SD of 24-hour BP and found that amlodipine and indapamide SR were effective antihypertensive agents in reducing BPV, independent of mean BP, in different time frames and modes.

BPV is a multifaceted phenomenon influenced by human activity, psychology, compliance to antihypertensive treat-

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**Table 3. Determinants of Systolic Blood Pressure Variability in Subjects at Baseline**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Daytime SD</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>Partial $R^2$</td>
<td>$P$</td>
<td>β</td>
<td>Partial $R^2$</td>
<td>$P$</td>
<td>β</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.06</td>
<td>0.03</td>
<td>$&lt;0.001$</td>
<td>0.07</td>
<td>0.03</td>
<td>$&lt;0.001$</td>
<td>0.07</td>
</tr>
<tr>
<td>Mean SBP, mm Hg</td>
<td>0.06</td>
<td>0.05</td>
<td>$&lt;0.001$</td>
<td>0.01</td>
<td>0.01</td>
<td>0.14</td>
<td>0.05</td>
</tr>
<tr>
<td>HR SD, bpm</td>
<td>0.21</td>
<td>0.02</td>
<td>$&lt;0.001$</td>
<td>0.29</td>
<td>0.04</td>
<td>$&lt;0.001$</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Age, sex, and body mass index, as well as mean systolic blood pressure, mean heart rate, and its variability calculated with the same algorithm in the same period as blood pressure variability, were considered in the linear regression models. SBP indicates systolic blood pressure; HR, heart rate; ARV, the read-to-read average real variability, which was calculated by the formula mentioned in the Methods. Daytime SD = time-weighted SD of 24-h systolic blood pressure readings during awake time; nighttime SD = time-weighted SD of 24-h systolic blood pressure readings during sleeping time; Daily SD = ([daytime SD × awake time] + [nighttime SD × sleeping time]) /(awake time + sleeping time).
duration. However, with the significant reduction in BPV frames and modes. The study’s limitations were the relatively double-blind, placebo-controlled design, enabling comparison, and the nervous and humoral systems, and reflects the determinants of BPV were investigated in several population studies, in which age, BP, HR, and sex were frequently reported. In the present study, we also indicated that age and BP were major determinants of BPV. We also took HRV into account and found that it was another important factor of BPV. From a physiological point of view, autonomic nervous system (ANS) regulates BP and HR synchronously and, therefore, contributes to stabilizing their fluctuation. The close association of BPV with HRV in different time frames is probably a universal phenomenon, which could be a consequence of the ANS regulation. Furthermore, the significant relationship between the reduction in BPV and in HRV, consistently observed in the present study, indicates a proportional decrease in the fluctuation of both BP and HR, which is probably attributable to amelioration of the ANS regulation. However, the pharmaceutical mechanism is still unknown.

In literature, there is limited information concerning the underlying mechanism of reduction in BPV. In the amlodipine group of the present study, we found that the reduction in BPV was mainly attributed to the reduction in BP and the reduction in HRV. On the other hand, in the indapamide SR group, we only found limited information with regard to determinants of the reduction in BPV. This difference indicates the distinct mechanism of those 2 antihypertensive agents. In the present study, we found that the effect of amlodipine on BPV was probably attributable to lowering BP and ameliorating the ANS regulation, whereas mechanism of indapamide SR in reducing BPV is largely unknown. Dabire et al. reported that, in spontaneous hypertensive rats, increased BPV was significantly associated with arterial stiffening. The similar finding was also achieved in sinoaortic-denervated rats by Lacolley et al. However, whether indapamide SR could possibly reduce BPV through arterial distiffening is still unclear, and further studies are warranted.

The strengths of the present study include the randomized, double-blind, placebo-controlled design, enabling comparison among the 4 treatment groups, and in 4 different time frames and modes. The study’s limitations were the relatively small number of subjects and the relatively short therapeutic duration. However, with the significant reduction in BPV after 3-month treatment, we had sufficient statistical power to confirm our findings.

**Perspectives**

In this study, we have shown that age, BP, and HRV were the major determinants of BPV. Amlodipine and indapamide SR were the only effective antihypertensive agents in decreasing BPV by lowering BP or ameliorating the ANS regulation or both. Their combination might help to optimize such properties. However, the mechanism underlying the reduction in BPV has yet to be clarified, especially its potential interaction with arterial stiffness and/or reflection waves. Given the increasing importance of BPV in the prevention of stroke, as well as other target-organ damage, further studies are undoubtedly warranted.

**Acknowledgments**

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**Disclosures**

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**References**


4. Bjorklund K, Lind L, Zethelius B, Berglund L, Lithell H. Prognostic significance of 24-h ambulatory blood pressure characteristics for cardio-

### Table 4. Determinants of the Reduction of Systolic Blood Pressure Variability by Amlodipine and Indapamide Sustained Release

<table>
<thead>
<tr>
<th>Variables</th>
<th>Daytime SD Reduction</th>
<th>Nighttime SD Reduction</th>
<th>Daily SD Reduction</th>
<th>ARV Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>Partial R²</td>
<td>P</td>
<td>β</td>
</tr>
<tr>
<td>Mean SBP reduction, mm Hg</td>
<td>0.08</td>
<td>0.06</td>
<td>0.005</td>
<td>0.02</td>
</tr>
<tr>
<td>HR SD reduction, bpm</td>
<td>0.19</td>
<td>0.04</td>
<td>0.02</td>
<td>0.46</td>
</tr>
<tr>
<td>Subjects taking indapamide SR (n=133)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean SBP reduction, mm Hg</td>
<td>0.04</td>
<td>0.02</td>
<td>0.14</td>
<td>0.01</td>
</tr>
<tr>
<td>HR SD reduction, bpm</td>
<td>0.01</td>
<td>0.01</td>
<td>0.89</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Age, sex, body mass index, as well as systolic blood pressure reduction and the reduction of heart rate variability calculated with the same algorithm in the same period as blood pressure variability, were considered in the linear regression models. Reduction indicates the after-treatment value minus the corresponding value at baseline. SBP indicates systolic blood pressure; HR, heart rate; ARV, the read-to-read average real variability, which was calculated by the formula mentioned in the Methods. Daytime SD=time-weighted SD of 24-h systolic blood pressure readings during awake time; nighttime SD=time-weighted SD of 24-h systolic blood pressure readings during sleeping time; daily SD=(daytime SD×awake time + nighttime SD×sleeping time)/(awake time + sleeping time).
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