Clinical Trial–INVEST

Blood Pressure Control and Improved Cardiovascular Outcomes in the International Verapamil SR-Trandolapril Study

Giuseppe Mancia, Franz Messerli, George Bakris, Qian Zhou, Annette Champion, Carl J. Pepine

Abstract—Uncontrolled blood pressure (BP) increases cardiovascular risk, independent of type of treatment. In this posthoc International Verapamil SR-Trandolapril Study analysis, we determined whether adverse outcomes are related to consistency of BP control, defined as the proportion of visits in which BP was in control. A total of 22 576 patients with hypertension and coronary artery disease were divided into 4 groups according to the proportion of visits in which BP was in control (<140/90 mm Hg): <25%, 25% to <50%, 50% to <75%, and ≥75%. Risk of primary outcome (first occurrence of death, nonfatal myocardial infarction, or nonfatal stroke), myocardial infarction, and stroke decreased progressively from the group with <25% to the group with ≥75% of visits with BP control. Adjusted risks of primary outcome (heart rate: 0.60; 95% CI: 0.53 to 0.67), myocardial infarction (heart rate: 0.58; 95% CI: 0.48 to 0.70), and stroke (heart rate: 0.50; 95% CI: 0.37 to 0.67) were less in the group with ≥75% of visits with BP control compared with the group with <25% of visits with BP control. Baseline BP was not predictive of outcomes. Proportion of visits with BP control was associated with mean follow-up systolic BP ($r^2=0.64$), both being independently related to primary outcome. As proportion of visits with BP control increases, there is an associated steep reduction in cardiovascular risk, independent of baseline characteristics and mean on-treatment BP. Consistency of BP control during treatment provides additional information on the protective effect of antihypertensive treatment. Physicians need to be concerned at each visit if BP is not controlled. (Hypertension. 2007;50:299-305.)

Key Words: hypertension ■ blood pressure control ■ antihypertensive treatment ■ antihypertensive drugs ■ blood pressure measurement/monitoring ■ clinical trials

Several lines of evidence support the view that blood pressure (BP) lowering, per se protects hypertensive patients, no matter how it is obtained. First, regardless of the treatment used, cardiovascular morbidity and fatal events are less in patients in whom on-treatment BP is reduced <140/90 mm Hg than in those in whom on-treatment BP remains uncontrolled.1-4 Second, regardless of the treatment used, in diabetic or other high-risk individuals, cardiovascular protection is greater if on-treatment BP values <130/80 mm Hg are achieved.5-9 Third, there is a type of treatment-independent relationship between the magnitude of the mean BP change throughout the treatment period and the incidence of cerebrovascular and coronary events.10,11

Analysis of BP control using mean follow-up BP does not provide a complete picture of BP control during a study, because BP may be in control at one visit and not in control at the next visit or vice versa. In the ELSA Study, for example, the number of patients with BP control at any given annual visit was much greater than the number of patients with consistent BP control at all 4 of the annual visits.12 The purpose of this posthoc analysis of the large database provided by the INternational VErapamil SR-Trandolapril (INVEST) prospective trial was to determine whether study outcomes are related to the consistency of BP control, defined as the proportion of visits in which BP is <140 mm Hg systolic and 90 mm Hg diastolic. It was thought that this approach, which, as far as we know, has not been used before, might provide an index of the consistency of BP control during treatment follow-up in addition to that provided by assessing on-treatment BP values, possibly adding information of prognostic relevance.

Methods

The INVEST Study design, treatment algorithm, and results have been reported previously.3,13 Briefly, INVEST randomly assigned 22 576 patients with essential hypertension (defined as requiring drug therapy by the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure14) and coronary artery disease to a verapamil-SR- or an atenolol-based strategy with the aim of achieving the BP control targets recommended by the Sixth Report of the Joint

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National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure guidelines (BP <140/90 mm Hg or BP <130/85 mm Hg for diabetes or renal impairment). At entry, most (87%) INVEST patients were receiving antihypertensive medication. After random assignments, visits were scheduled at weeks 6, 12, 18, and 24 and every 6 months thereafter. Average patient follow-up was 2.7 years. The primary outcome was the first occurrence of death, nonfatal myocardial infarction (MI), or nonfatal stroke. In the present analysis, INVEST patients randomly assigned to the 2 treatment strategies were pooled and then divided into 4 groups according to the proportion of visits in which BP was <140 mm Hg systolic and 90 mm Hg diastolic, defined as in control: <25%, 25% to <50%, 50% to <75%, and ≥75%. Mean follow-up BP used BP measurements from all of the postbaseline visits before primary outcome or censoring. For patients with no postbaseline data, baseline BP measurements were used. Demographic (age, gender, and ethnicity) and clinical variables (body mass index, history or presence of cardiovascular disease, smoking, hypercholesterolemia, diabetes, and cardiovascular medications) were calculated for the 4 BP control groups. This was done also for baseline BP, follow-up BP, and outcomes. Stepwise Cox proportional hazard models were used to estimate the risk of primary outcome, nonfatal and fatal MI, and nonfatal and fatal stroke, with the group with <25% of visits in control as the reference. Adjustments for baseline characteristics were made by forcing 5 prespecified covariates into the stepwise model (age, gender, race, previous MI, and heart failure) and selecting other covariates with a \( P \leq 0.10 \). Similar analyses were conducted for the subgroup of patients (n=6400) with diabetes at baseline. Stepwise Cox models were also used to separately analyze the effect of baseline BP, mean follow-up BP, and baseline hypercholesterolemia (defined as a history of hypercholesterolemia and/or use of lipid-lowering agent) and antiplatelet treatment on the risk of primary outcome in relation to the proportion of visits with BP control. Data are shown in percentage or as mean±SD. A \( P \leq 0.05 \) was taken as the level of statistical significance.

**Results**

**Baseline Characteristics**

Table 1 shows the baseline characteristics of patients with BP control in <25% to ≥75% of visits. Baseline characteristics differed among the 4 groups. Patients in the group with <25% of visits in control were more likely to be older, female, black, US resident, have higher body mass index, and have diabetes and were less likely to be Hispanic, smokers (ever), have hypercholesterolemia, or use nitrate or aspirin compared with patients in the group with ≥75% of visits in control.

**BP**

As shown in Table 2, mean baseline BP was progressively lower from the group in which the proportion of visit with BP control was <25% to the group in which it was ≥75%. All 4 of the groups experienced a BP reduction from baseline, defined as the difference between mean baseline and mean follow-up BP. The size of the reduction increased progressively from patients with <25% to those with 50% to <75% of visits in control, with no further antihypertensive effect for those with ≥75% of visits in control. Baseline nitrate use was...
highest in the group with ≥75% of visits in control. Within each BP control group, follow-up BP was similar for patients with and without baseline nitrate use (data not shown).

Clinical Outcomes
Clinical outcome rates (primary outcome, MI, and stroke) declined as the proportion of visits with BP control increased (Figure 1). Results were similar for both treatment strategies (data not shown). This relationship persisted when the outcome risks were adjusted for differences in baseline conditions (Figure 2). The adjusted risk of primary outcome, MI, and stroke was less (40%, 42%, and 50%, respectively) in the group with ≥75% of visits with BP control compared with the group with <25% of visits with BP control. The greatest difference in outcomes between groups with different proportions of visits with BP control was observed for the risk of stroke, though this was the least frequent outcome. Baseline hypercholesterolemia was associated with a lower risk of primary outcome (adjusted HR: 0.81; 95% CI: 0.75 to 0.89; P < 0.001). When baseline aspirin/antiplatelet use was forced into the model, there was no association with risk of primary outcome (adjusted HR: 1.01; 95% CI: 0.92 to 1.11; P = 0.86). In the group with ≥75% of visits in control, the primary outcome rate was lower when BP control was defined using Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure goals (7.4%) versus 140/90 mm Hg (8.1%).

As shown in Figure 3, in patients with diabetes at baseline, the percentage of patients in the 2 categories with the lowest proportion of visits with BP in control was slightly greater than in patients without diabetes at baseline (Figure 3, top). Patients with diabetes had a higher rate of primary outcome than patients without diabetes in each BP control group (P < 0.001; Figure 3, bottom). The rate of primary outcome decreased as the proportion of visits in control increased both in patients with and in patients without diabetes at baseline (P for trend < 0.001). Among diabetic patients, the adjusted risks of primary outcome (HR: 0.59; 95% CI: 0.50 to 0.71), MI (HR: 0.59; 95% CI: 0.45 to 0.78), and stroke (HR: 0.45; 95% CI 0.27 to 0.74) were less in the group with ≥75% of visits with BP control compared with the group with <25% of visits with BP control.

<table>
<thead>
<tr>
<th>Variable</th>
<th>&lt;25%</th>
<th>≥25% to &lt;50%</th>
<th>≥50% to &lt;75%</th>
<th>≥75%</th>
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</thead>
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<td>No. of patients</td>
<td>3838*</td>
<td>3757</td>
<td>6664</td>
<td>8316</td>
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<tr>
<td>Mean baseline SBP (SD)</td>
<td>161.7 (18.0)</td>
<td>156.0 (17.8)</td>
<td>152.2 (17.6)</td>
<td>142.4 (18.8)</td>
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<tr>
<td>Mean baseline DBP (SD)</td>
<td>90.0 (12.1)</td>
<td>87.9 (11.6)</td>
<td>88.0 (11.6)</td>
<td>84.8 (11.9)</td>
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<tr>
<td>Mean follow-up SBP (SD)</td>
<td>155.3 (13.6)</td>
<td>142.1 (7.4)</td>
<td>133.2 (7.1)</td>
<td>125.1 (6.6)</td>
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<td>Mean follow-up DBP (SD)</td>
<td>85.9 (10.1)</td>
<td>80.5 (6.9)</td>
<td>78.1 (6.0)</td>
<td>75.5 (5.4)</td>
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<td>6.4</td>
<td>13.9</td>
<td>19.0</td>
<td>17.3</td>
</tr>
<tr>
<td>DBP reduction</td>
<td>4.1</td>
<td>7.4</td>
<td>9.9</td>
<td>9.3</td>
</tr>
</tbody>
</table>

SBP indicates systolic BP; DBP, diastolic BP. BP reduction = mean baseline BP – mean follow-up BP.
*One subject had no BP measurement before primary outcome and was excluded from this analysis.

**Figure 1.** Unadjusted clinical outcomes by proportion of visits with blood pressure control. Data are shown as percentages.
Impact of Baseline BP, Mean Follow-Up BP, and BP Reduction

There was some association between baseline SBP and the proportion of visits in control (correlation coefficient $r = 0.41$; $r^2 = 0.17$). In a model that adjusted for differences in baseline characteristics, baseline SBP (HR: 1.00; 95% CI: 1.00 to 1.00; $P = 0.23$) and baseline DBP (HR: 1.00; 95% CI: 0.99 to 1.00; $P = 0.52$) were not associated with an increased risk of primary outcome.

Patients with a progressively lower proportion of visits with BP control had a progressively higher mean follow-up SBP (from 125.1 mm Hg to 155.3 mm Hg) from the group with $\geq 75\%$ to the group with $< 25\%$ of the visits with BP control). These 2 BP variables were strongly associated with each other (correlation coefficient $r = 0.80$; $r^2 = 0.64$). In an exploratory stepwise Cox proportional hazard model, proportion of visits with BP control (as a continuous variable) and mean follow-up SBP were both predictive of primary outcome when simultaneously included in the model ($P < 0.001$ for both variables). Patients with a higher proportion of visits with BP control had lower incidences of primary outcome ($P$ for trend $< 0.001$) regardless of whether their baseline BP or BP reduction was above or below the median value (Figure 4).

Discussion

The present posthoc analysis of data from the INVEST trial shows that the risk of cardiovascular morbidity and mortality, as well as the risk of MI and stroke, was inversely related to the proportion of on-treatment visits in which BP was found to be controlled, ie, clinic values were $< 140/90$ mm Hg systolic and $90$ mm Hg diastolic. These data also indicate that the relationship between the risk of fatal and nonfatal events and the proportion of visits with BP control persisted after adjustment for differences in baseline demographic, as well as clinical and therapeutic, characteristics between groups with different proportions of visits in which BP was controlled, including baseline BP. Finally they show that, although the proportion of visits with BP control and the mean BP level during the treatment period were related to each other, the incidence of fatal and nonfatal cardiovascular events was independently associated with either variable. Our data confirm the results from other studies that the extent to which antihypertensive treatment protects hypertensive patients from cardiovascular disease is associated with the mean BP level achieved during treatment, with lower rates of events when a mean BP $< 140/90$ mm Hg is achieved. A new finding, however, is that an additional factor seems to be how often during the treatment period BP achieves adequate control. We can advance the hypothesis that this originates from the fact that the number of visits in which BP is $< 140/90$ mm Hg provides information on the temporal pattern of BP control during treatment, ie, that finding BP values $\geq 140/90$ mm Hg at a given visit reflects absence of BP control (and, thus, greater cardiovascular risk). The recent report from the Perindopril Protection Against Recurrent Stroke Study that stroke was more common during the months before detection of higher as compared with lower BP9 supports this hypothesis.

Several other results of our study deserve to be mentioned. First of all, the more common occurrence of baseline hypercholesterolemia in patients with $\geq 75\%$ of the visits with BP control could have been responsible for their more favorable outcome, because hypercholesterolemia had an inverse relationship with the incidence of death and cardiovascular events, presumably because of its association with the use and protection provided by statins. However, differences in outcome in relation to the percentage of visits with BP
control were also seen in the remaining 3 groups in which there were no or trivial differences in hypercholesterolemia, which makes this explanation unlikely. Second, the results on the prognostic importance of constancy of BP control obtained in the overall INVEST population were duplicated in the large subgroup of diabetic patients for whom the above conclusions also apply. Third, in the INVEST trial, on-treatment average BP was 135/79 mm Hg, \(^3\) ie, well below the level of 140/90 mm Hg regarded as reflecting effective treatment and recommended by the guidelines.\(^{17,18}\) However, a noticeable proportion of visits showed BP to be uncontrolled in a large number of patients, 34% of which failed to show control in more than half of the visits. This suggests that averaging BP over the treatment period may overestimate the effectiveness of treatment and mask time intervals during which BP control is not achieved, with undesirable consequences for patient protection and prognosis. Fourth, patients with the lowest proportion of visits with BP control were more likely to be older, black, overweight, and diabetic than patients with the highest proportion of BP control. This confirms that the above conditions make BP control more difficult,\(^{18-21}\) adding that this is the case also when not only the degree of average BP reduction but the consistency of BP control over time is considered. Fifth, baseline systolic and diastolic BPs were progressively lower as the proportion of visits with BP control progressively increased, which means that, predictably, it was easier to lower BP <140/90 mm Hg if its initial value was not too high. However, neither systolic nor diastolic baseline BP correlated with the primary outcome (death and cardiovascular disease), MI, or stroke, in striking contrast with the prognostic relevance of achieved BP. This confirms the conclusions of previous trials that pretreatment is prognostically less important than on-treatment BP,\(^{22,23}\) of which control can modify a patient’s risk and fate within few years even when, as for the INVEST patients, initial cardiovascular risk is high and cardiac damage already clinically manifest. Sixth, the number of visits in which BP was controlled was related to average on-treatment BP, which may explain why the 2 groups in which control was more frequent had the greatest BP reduction. However, in a multivariate analysis, frequency of BP visits in control was related to outcome, independent of on-treatment BP values. Seventh, in the group with the greatest proportion of visits in control, the primary outcome rate was lower when BP control was defined using Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure goals instead of 140/90 mm Hg, demonstrating the benefit of the lower BP targets for patients with diabetes or renal impairment. Finally, it should be remembered that the present data were obtained by a posthoc analysis of a prospective randomized trial, a

![Figure 3. Distribution of patients and unadjusted primary outcome rate by proportion of visits with BP control: patients without and with diabetes at baseline. For symbols and explanation see Figure 1.](http://hyper.ahajournals.org/content/full/303/50/301/F3)
limitation that requires the conclusions to be taken with a degree of caution.

Perspectives
Our posthoc analysis suggests that the percentage of visits in which BP is controlled by treatment represents an indicator of the degree of patients’ protection independent of and in addition to the magnitude of overall BP reduction and the BP level achieved during the treatment period. This has implications for both clinical trials and clinical practice. Focusing on both on-treatment average BP and on the proportion of visits with BP control may improve the assessment of the protective effect of BP-lowering interventions in patient outcome trials, possibly by the addition of indirect information on the time spent under control. The proportion of visits with BP in control may also offer the practicing physician a simple index to retrospectively and/or prospectively characterize patient BP control over time and provide a better insight into the cardiovascular risk reduction achieved by treatment. It would appear from our data that this index has value in the presence of both large and small overall BP reductions, calling in both instances for more intensive BP treatment and increased emphasis on drug adherence.

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References


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