Influence of Diabetes and Type of Hypertension on Response to Antihypertensive Treatment

Morris J. Brown, Alain Castaigne, Peter W. de Leeuw, Giuseppe Mancia, Christopher R. Palmer, Talma Rosenthal, Luis M. Ruilope

Abstract—The aim of our investigation was to determine whether the presence of additional risk factors or type of hypertension (diastolic or isolated systolic) influences blood pressure (BP) response to treatment. The International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) study is a double-blinded outcome comparison of calcium channel blockade with diuretics in high-risk patients aged 55 to 80 years. Dynamic randomization between nifedipine once daily and hydrochlorothiazide/amiloride was performed to ensure that approximately equal numbers of patients in the 2 groups had each of the major cardiovascular risk factors. Patients with isolated systolic hypertension were also separately randomized. Atenolol or enalapril was the mandatory second-line drug. In 5669 patients who completed the 18-week titration, BP fell from 172±15/99±9 mm Hg (mean±SD) while receiving placebo to 139±12/82±7 mm Hg. Twenty-six percent of patients required 2 drugs, and 4% required 3 drugs. Patients with diabetes were the most resistant to treatment, requiring second and third drugs 40% and 100% more frequently than patients without diabetes and achieving marginally the highest final BP, for any risk group, of 141±13/82±8 mm Hg. Age, smoking, gender, hypercholesterolemia, left ventricular hypertrophy, and existing atherosclerosis had little (<1 mm Hg) or no influence on BP at the end of titration, but all except smoking slightly reduced the initial response of either systolic or diastolic BP. Patients with isolated systolic hypertension were slightly more responsive than average to treatment. Our findings suggest that in patients at high absolute risk of cardiovascular complications from hypertension, the risk factors themselves do not prevent the recommended BP targets from being achieved. (Hypertension. 2000;35:1038-1042.)

Key Words: cardiovascular diseases □ diabetes mellitus □ random allocation □ antihypertensive therapy □ calcium channel blockers □ diuretics

Some 200 000 patients are currently participating in outcome trials comparing most permutations of old and new antihypertensive agents.1 Although the primary question these trials ask is whether there is a difference in outcome between drugs or regimens, it is likely that the major, overall determinants of outcome will be blood pressure (BP) before treatment, BP during treatment, and other measures of risk or target organ damage.2,3 Although the clustering of hypertension with other cardiovascular risk factors is well known, together with the multiplication of cardiovascular risk when these are present simultaneously, there is little information about the relative efficacy of antihypertensive treatment in the presence of other risk factors.4 Clearly, BP can be reduced in groups such as smokers and diabetics and in patients with isolated systolic hypertension (ISH), left ventricular hypertrophy (LVH), or evidence of atherosclerosis. But the clustering of such factors means that a large number of patients with and without each of these conditions is required to answer, without confounding, simple questions like “Do diabetics need more treatment than nondiabetics to achieve a given reduction in BP?” “Can the systolic BP (SBP) in ISH be reduced as easily as in non-ISH?” and “Are there patients with ISH in whom antihypertensive treatment is more likely to cause excessive reduction of diastolic (DBP)?” Such questions have become more pressing with the publication of trials suggesting the long-term safety and efficacy of reducing BP to normal levels, especially in high-risk groups like diabetics, and the incorporation of recommendations to this effect in the latest World Health Organization–International Society of Hypertension guidelines.5

The opportunity to answer such questions has arisen within current outcome trials, which have recruited mostly high-risk patients so that sufficient events will accrue to have the power to detect differences.1 The stage of blinded treatment permits

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investigators to establish, irrespective of type of treatment, whether the type of patient influences efficacy of antihypertensive treatment. Subsequently, the planned World Health Organization—International Society of Hypertension meta-analysis of all current trials will enable the success of individual treatments in preventing each complication of hypertension in each risk group to be compared.

Trials able to undertake a cogent examination of antihypertensive efficacy by risk group are those in which the treatment is double-blinded and patients are stratified by each risk group before randomization. This means that initial treatment can be assumed, without breaking the blinding, to be allocated in equal proportions among the primary drugs; this assumption in turn allows the influence of patient characteristics in response to treatment to be analyzed without regard to the type of treatment. Preferably, the primary drugs should be long-acting agents, with high trough/peak ratios, to avoid the pitfalls of interpreting differences in BP because of the variable times of visits after dosing that are usual in an outcome trial.6 The International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) study was among the first of these studies, initiated in 1994 in high-risk, mainly white hypertensives, and will report its results in June 2000.7,8 The primary drugs in INSIGHT are a long-acting calcium channel blocker, nifedipine once daily (GITS), and a diuretic combination, hydrochlorothiazide and amiloride. These classes are, arguably, the drugs of choice for older age groups, both for overall antihypertensive efficacy and demonstrated efficacy against placebo in patients with both diastolic hypertension and ISH.9–12 In INSIGHT, an average treated BP of <140/85 mm Hg was achieved, with 68% of patients requiring only 1 drug.3 The aim of the analyses was to determine, within a study powered to permit multiple comparisons of risk groups, whether BP responsiveness is impaired in any of these risk groups and whether BP control can be achieved in these groups by the addition of extra therapy.

**Methods**

The design of INSIGHT was previously described.7 In brief, 6418 patients aged 55 to 80 years from 9 countries, with SBP >150 mm Hg and DBP >95 mm Hg or SBP >160 mm Hg and DBP <95 mm Hg after 2 to 4 weeks on placebo were randomly assigned to receive GITS 30 mg daily or a combination tablet containing hydrochlorothiazide 25 mg and amiloride 2.5 mg, 1 tablet daily. Treatment was titrated over the next 18 weeks. The target of treatment was 140/90 mm Hg and/or a 20/10-mm Hg fall in BP. Dose doubling of the randomized drug was permitted after 2 weeks; atenolol 25 to 50 mg or enalapril 5 to 10 mg (if ß blockade was contraindicated) could be added after 4 or 8 weeks, respectively. After 12 weeks of treatment, any other drug (excluding diuretics or calcium channel blockers) could be added. All additional treatments were open labeled. Patients were seen at 4-month intervals after the 18th week of active treatment, and treatment changes continued at these visits to pursue or maintain the BP goal.

Apart from the BP entry criteria, patients were required to have at least 1 additional major risk factor for cardiovascular disease. A list of these is shown in Table 1, together with the proportion of patients eventually recruited with each. Patients were prestratified both by these risk factors and by gender, country, age group (≥ 65 years), aspirin use, and type of hypertension (diastolic or ISH) before dynamic treatment randomization, sometimes called a minimization

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercholesterolemia*</td>
<td>3352</td>
<td>52.0</td>
</tr>
<tr>
<td>Smoker†</td>
<td>1863</td>
<td>28.9</td>
</tr>
<tr>
<td>Family history‡</td>
<td>1356</td>
<td>21.0</td>
</tr>
<tr>
<td>Diabetes mellitus (type 1 or 2)</td>
<td>1312</td>
<td>20.3</td>
</tr>
<tr>
<td>LVH§</td>
<td>674</td>
<td>10.4</td>
</tr>
<tr>
<td>CHD(</td>
<td>402</td>
<td>6.2</td>
</tr>
<tr>
<td>Left ventricular strain¶</td>
<td>398</td>
<td>6.2</td>
</tr>
<tr>
<td>Previous MI</td>
<td>386</td>
<td>6.0</td>
</tr>
<tr>
<td>PVD#</td>
<td>359</td>
<td>5.6</td>
</tr>
<tr>
<td>Proteinuria**</td>
<td>170</td>
<td>2.6</td>
</tr>
</tbody>
</table>

*Plasma total cholesterol of ≥6.43 mmol/L (250 mg/dL) at study entry.
†Smoked ≥10 cigarettes/day currently or up to 1 y before entry.
‡MI in parent or sibling before the age of 50 y.
§Echocardiographic diagnosis.
¶Stable angina or asymptomatic CHD, confirmed by coronary angiographic evidence or ECG changes on exercise testing.
#Interruption claudication, resting pain, or gangrene (ie, Fontaine and Leriche classification stages 2–4).
**Measurement of ≥0.5 g protein/24 h.

**Statistical Analyses**

The influence of all variables in Table 2 on initial BP response, after 2 weeks of the lower dose of the primary drug, was estimated by multiple regression analyses. In these analyses, the difference between baseline and 2-week BPs (BP1 and BP 2, respectively) was estimated by multiple regression analyses. In these analyses, the difference between baseline and 2-week BPs (BP1 and BP 2, respectively) was corrected by the Oldham formula, (BP 2 − BP1)/2, to remove the mathematical correlation between ΔBP

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>β</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>0.076</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SBP</td>
<td>−0.26</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DBP</td>
<td>0.07</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>0.067</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVH</td>
<td>0.057</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.045</td>
<td>0.0016</td>
</tr>
<tr>
<td>DBP</td>
<td>−0.31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SBP</td>
<td>0.10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>0.11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVH</td>
<td>0.043</td>
<td>0.0028</td>
</tr>
<tr>
<td>Gender</td>
<td>0.036</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*All additional risk factors and other variables used in the minimization program were entered stepwise into a multiple regression, in which the dependent variables were ΔSBP1 and ΔDBP1 (see Methods for Oldham correction formula). In this formula, falls in SBP were negative values, so positive coefficients are shown for factors associated with an attenuated fall in BP. To allow for multiple comparisons, only variables with a P < 0.005 are shown.
and baseline BP and was used as the dependent variable in a multiple regression analysis on the stratification variables, omitting age group. Age and placebo readings for SBP and DBP were included among the independent variables. Patients included in the regression analyses were the 6388 who attended the first postrandomization visit.

The influence of each risk factor on the final response at the end of treatment titration was estimated by repeated-measures ANOVA in the 5669 patients who were still receiving randomized treatment at the end of treatment titration. Dependent variables were the sequential SBP or DBP values while receiving placebo and at the next 5 visits up to 18 weeks (omitting the 10-week visit for optional titration of atenolol or enalapril). Independent variables were the stratification variables, and to reduce the chance of false-positive results due to multiple comparisons, some of the less frequent variables were treated independently of each other. Thus, only baseline SBP predicted DBP, but LVH and atherosclerosis significantly reduced responsiveness. Even after the mathematical correlation between DBP and baseline BP was removed with the Oldham correction, the latter variable was the major determinant of response. Interestingly, however, SBP and DBP behaved almost the same final BP, Table 4 shows even smaller pressure than nondiabetics and required significantly more treatment to achieve a final BP of 141±13/82±8 mm Hg. There were also minor, but statistically significant, differences between risk groups in the initial BP response to treatment.

Results of the multiple regression analysis of initial BP response on all stratification variables are presented in Table 2. The variables most likely to cause target organ damage, smoking and cholesterol, had little or no influence on ΔSBP or ΔDBP, but LVH and atherosclerosis significantly reduced responsiveness. Even after the mathematical correlation between ΔBP and baseline BP was removed with the Oldham correction, the latter variable was the major determinant of response. Interestingly, however, SBP and DBP behaved independently of each other. Thus, only baseline SBP predicted ΔSBP, and, similarly, only baseline DBP predicted ΔDBP; indeed, regression analysis showed that baseline SBP and DBP inversely correlated with ΔDBP and ΔSBP, respectively. This finding predicted that pulse pressure would have opposing influences on ΔDBP and ΔSBP, and this prediction was confirmed by entering pulse pressure instead of SBP and DBP into the regression equation.

Results for patients with diabetes and ISH are shown in more detail. Table 3 shows that diabetics have a wider pulse pressure than nondiabetics; however, when they receive significantly more treatment, diabetics manage to achieve almost the same final BP. Table 4 shows even smaller differences between patients with and without ISH, with no significant difference in numbers receiving added treatment. Figures 1 and 2 illustrate, for patients with diabetes and ISH, respectively, the closeness of BP response to treatment when the repeated-measures ANOVA corrects for known relevant variables.

For other risk factors, there were no differences in final achieved BP. The average final treatment step for all patients in the trial (with steps 1 and 2 being monotherapy; 3 and 4,
dual therapy; and 5, triple therapy) was 2.08. This average was significantly higher in patients with PVD, previous MI, family history of MI, LVH, and proteinuria, although none reached the 10% excess seen in patients with diabetes (Table 3). Smoking, gender, cholesterol, age group, ISH, and CHD had no significant influence.

The repeated-measures analyses also disclosed a number of interesting interactions among risk factors, of which only the 2 most significant and striking are reported. The first finding was that the fall in both SBP and DBP was twice as great in patients with atherosclerosis but no hypercholesterolemia than in patients with both risk factors (17.5/7.5 versus 8.5/3.0 mm Hg, \( P = 0.005 \)); in patients without atherosclerosis, cholesterol had no influence on BP response. The second finding, illustrated in Figure 3, was that patients with ISH who fail to maintain their DBP with increasing therapy are smokers with existing evidence of atherosclerosis.

Plots from the repeated-measures analysis also shed some light on the nature of the patients who appear to be poor responders. Figure 4 shows BP responses for patients divided according to the final dose step achieved. Inspection of the traces for patients requiring higher dose steps shows that although a higher baseline BP overall predicted a greater fall in BP (Table 1), the reverse was true for poor responders. They displayed a small but cumulative response to each step, although the effect of adding a drug (steps 3 and 5) was greater than that of increasing the dose.

**Discussion**

The large numbers of patients with multiple risk factors in this study and dynamic randomization for each risk factor permitted a valid investigation into the independent influence of these factors on BP response. Previous outcome trials have included patients with additional risk factors, but these patients have been a smaller proportion, have not been separately randomized, and (except for the smokers in the Medical Research Council mild hypertension trial) have not generally been the subject of separate BP response analyses. INSIGHT included almost 25% each of diabetic and ISH patients; because the comparison (as in most current trials) is between 2 active drug groups, all patients provide data on response to treatment.

The 2 main cardiovascular risk factors, cholesterol and smoking, were found to have little or no effect, respectively. The 2 irreversible factors, age and gender, had no influence on SBP response; DBP was slightly more responsive in women and older patients. The various categories of target organ damage were associated in most of the statistical tests with slight resistance to treatment. Interestingly, when CHD, PVD, and previous MI were considered separately, CHD had no influence. This may be because isolated CHD that has not led to an unstable event is less likely to be associated with systemic abnormalities such as impaired endothelial function; however, it is also possible that the patients with CHD in INSIGHT have relatively mild disease because the use of \( \beta \) blockers or calcium channel blockers was an exclusion criterion for entry.
Diabetes and ISH were singled out for closer analysis because of the interest in these as high-risk conditions, in which the value of aggressive BP control now appears well founded; indeed, the 10% of ISH patients in the Syst-Eur trial who were also diabetic derived significantly greater benefit from calcium channel blocker treatment than those who were nondiabetic.17 Our analyses showed that diabetics start with slightly higher pulse pressures than nondiabetics and require more treatment to achieve almost the same BP target as other patients; however, these differences are small and mainly emphasize the need to consider combination treatment in these patients, especially if aiming for even more stringent targets than in nondiabetics. We were fortunate that the patients recruited to INSIGHT with ISH were comparable in most baseline characteristics, including SBP, with other patients, validating the comparison of SBP responsiveness between ISH and other patients.

Apart from the primary analyses by patient risk group, the data provide a more descriptive look at patients who appear particularly responsive or unresponsive. The latter are, largely, patients requiring higher titration steps. Because titration was not forced, use of higher steps alone does not prove that the patients were unresponsive, because investigators were more likely to use additional therapy in patients with higher starting pressures or certain risk factors, such as diabetes. Indeed, Figure 4 shows that patients receiving higher increments had higher starting pressures. Yet overall, higher pressures were associated with a greater proportional response, whereas inspection of the figure shows that patients on the higher steps had proportionally smaller responses to each step than other patients. How is this paradox to be resolved? The answer probably lies in the degree of target organ damage, with LVH and atherosclerosis being more common in nonresponders and patients with higher baseline SBPs. There is also perhaps an indication from Figure 4 that true responders are qualitatively different from the rest, being those who achieve and sustain a normal BP within 1 visit of changing from placebo to the lowest dose of active treatment.

Acknowledgment

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References


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