Blood pressure-lowering drugs: essential therapy for some patients with normal blood pressure

Flávio D Fuchs

The risk of increasing blood pressure for the incidence of cardiovascular disease starts at 115/75 mmHg and roughly doubles for every 10 years increase in age, 20 mmHg increase in systolic blood pressure, 10 mmHg increase in diastolic blood pressure, or in the presence of co-morbidities, such as diabetes or any evidence of cardiovascular disease. To lower blood pressure of patients with normal blood pressure and diabetes, or heart failure, or with any evidence of atherosclerotic disease in the coronary, cerebral, and peripheral territories, reduces the incidence of major cardiovascular events by 18 to 42%. The diagnosis of hypertension in patients with these conditions is therefore irrelevant. ACE inhibitors are the drugs mostly tested in such conditions, but their efficacy probably derives from their blood pressure lowering effect, instead of a primary antiatherosclerotic effect.

The findings of this meta-analysis of observational studies explained the results of almost all trials that evaluated the efficacy of blood pressure-lowering drugs in the prevention of cardiovascular events for a wide range of blood pressure values. In the pioneering trial of the Veterans Administration [2], it was only necessary to treat six individuals with very high diastolic blood pressure in order to prevent one major cardiovascular event [3]. At moderately increased blood pressure levels, the number needed to be treated (NNT) in order to prevent a major event increased, as expected, to 35 [4]. In middle-aged individuals with mild hypertension, the NNT was 250 [5], decreasing to approximately 100 individuals in older individuals with diastolic [6,7] or isolated systolic hypertension [8,9]. Staessen and associates have repeatedly shown that the reduction in the incidence of cardiovascular events observed in clinical trials was proportional to the intensity of the observed decrease in blood pressure [10,11]. The superiority of chlorthalidone (Hygroton®, Alliance Pharmaceuticals Ltd) over other blood pressure-lowering drugs in the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) was primarily explained by its more efficacious blood pressure-lowering effect [12].
The implications of a higher risk for cardiovascular events in individuals with blood pressure levels within the normal range depend on the presence of other comorbidities and risks. The twofold increase in risk for an individual with very low baseline risk, such as a young adult, without diabetes and without evidence of cardiovascular disease, with a diastolic blood pressure of 85 mmHg, compared with an individual with a diastolic blood pressure of 75 mmHg, certainly does not necessitate pharmacological treatment. This individual should instead be informed of his/her higher risk, and of the benefits of several nonpharmacological interventions that may prevent the increase of their blood pressure with age.

In the presence of other comorbidities or diabetes, the twofold increase in risk caused by a 10 mmHg difference in diastolic or a 20 mmHg in systolic blood pressure has a more evident clinical consequence. Several clinical trials have shown that lowering blood pressure in individuals with higher cardiovascular risk and blood pressure within normal levels decreases the incidence of cardiovascular events by a sizeable and clinically significant proportion (Table 1).

The Heart Outcomes Prevention Evaluation (HOPE) study enrolled men and women who were at least 55 years old with a history of cardiovascular disease (coronary heart disease, stroke or peripheral vascular disease) or diabetes plus at least one major cardiovascular risk factor [13]. Almost 50% of the participants had hypertension, but the results in normotensive and hypertensive participants were similar to those observed in participants with hypertension. Patients with diabetes had the same protection irrespective of the diagnosis of hypertension [14]. Moreover, the incidence of microvascular outcomes was lowered by 16% (95% confidence interval [CI]: 1–29%). The overall 22% reduction in the incidence of the primary end point (stroke, myocardial infarction or cardiovascular death) was originally attributed to other effects of the angiotensin-converting enzyme (ACE) inhibitor, because the reduction of office blood pressure in patients treated with ramipril (Tritace®, Aventis Pharma Ltd) was slight. A small HOPE substudy, however, with ambulatory blood pressure monitoring, showed a large fall in blood pressure, especially at night, in patients treated actively, suggesting that the effect of ramipril could be ascribed mainly to the reduction in blood pressure [15].

The Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS) allocated patients with a previous episode of cerebrovascular disease to active treatment (perindopril [Coversyl®, Servier Laboratories Ltd] alone or associated with indapamide [Natrilix®, Servier Laboratories Ltd]) or placebo [16]. There was a 40% reduction in the recurrence of strokes in patients treated with the combination of the two drugs, but not with perindopril alone. This beneficial effect was independent of the baseline blood pressure, since it was observed in hypertensive and normotensive participants.

The EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) trial recruited patients with previous myocardial infarction, percutaneous or surgical coronary revascularization, or angiographic evidence of at least 70% narrowing of one or more of the major coronary arteries [17]. Men could also be enrolled if they had a history of chest pain and a positive electrocardiogram, echo, or nuclear stress test. There was a significant relative risk reduction of 20% (2% absolute) in the incidence of the primary end point (cardiovascular death, myocardial infarction or cardiac arrest) in patients treated with perindopril. These differences are among the predicted benefits of a blood pressure lowering effect of 5/2 mmHg in patients treated with perindopril, although this differs from the author’s statement.

### Table 1. Characteristics of the clinical trials that have tested the effect of blood pressure-lowering drugs in normotensive individuals.

<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>Active treatment</th>
<th>Primary outcome</th>
<th>Relative-risk reduction (95% CI)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus§</td>
<td>Ramipril</td>
<td>Myocardial infarction, stroke or cardiovascular death</td>
<td>25% [12–36]§</td>
<td>[14]</td>
</tr>
<tr>
<td>Evidence of atherosclerosis in the coronary, cerebral or peripheral territories</td>
<td>Ramipril</td>
<td>Myocardial infarction, stroke or cardiovascular death</td>
<td>22% [14–30]§§</td>
<td>[13]</td>
</tr>
<tr>
<td></td>
<td>Perindopril</td>
<td>Myocardial infarction, stroke or cardiovascular death</td>
<td>20% [9–29]§§</td>
<td>[17]</td>
</tr>
<tr>
<td>Recovered from stroke</td>
<td>Indapamide plus perindopril</td>
<td>Stroke</td>
<td>42% [19–58]§§</td>
<td>[16]</td>
</tr>
<tr>
<td>Asymptomatic heart failure</td>
<td>Enalapril</td>
<td>Cardiovascular death</td>
<td>12% [1–3–26]§</td>
<td>[18]</td>
</tr>
<tr>
<td>Overt heart failure</td>
<td>Enalapril</td>
<td>Cardiovascular death</td>
<td>18% [6–28]§</td>
<td>[19]</td>
</tr>
<tr>
<td></td>
<td>Captopril</td>
<td>Cardiovascular death</td>
<td>21% [5–35]§</td>
<td>[20]</td>
</tr>
</tbody>
</table>

§§In individuals at least 55 years old with another major cardiovascular risk factor (elevated cholesterol levels, low HDL-cholesterol, cigarette smoking, or microalbuminuria).

§§Estimate for the entire cohort, not significantly different between normotensive and hypertensive individuals.

CI: Confidence interval; HDL: High-density lipoprotein; MI: Myocardial infarction.
Variation in blood pressure was not a primary or secondary end point in trials that evaluated the effects of blood pressure-lowering drugs in patients with heart failure. Among the trials that reported the effect of active treatment on blood pressure, a clear-cut blood pressure-lowering effect was seen. In trials with overt and nonovert heart failure, the treatment with an ACE inhibitor lowered systolic blood pressure by 4.7 to 6.0 mmHg and diastolic by 3 to 4 mmHg compared with placebo [18–20]. In the comparison of lower and higher doses of lisinopril [21], the lower incidence of cardiovascular events in the higher dose group may be largely attributed to the reduction of 4.4/2.3 mmHg in systolic/diastolic blood pressure. The marginal advantage of enalapril over the association of hydralazine and isosorbide dinitrate in the Veterans Administration trial may be also ascribed to the 5/3 mmHg greater reduction of blood pressure in patients treated with enalapril [22].

The efficacy of β-blocker therapy to prevent morbid and fatal events in patients with heart failure is probably unrelated to their effects on blood pressure. Most trials did not report the effects of the active treatment on blood pressure [23–25], or did not show a major blood pressure difference between the active and control treatments [26]. A noticeable exception was the demonstration of the superiority of full doses of carvedilol (Eucardi®, Roche) over half-doses of metoprolol (Betaloc®, AstraZeneca) in the prevention of cardiovascular events in the Carvedilol Or Metoprolol European Trial (COMET) [27]. The lower incidence of certain end points in patients treated with carvedilol may, at least in part, be attributed to the significant 1.8 mmHg reduction in systolic blood pressure. The Randomized Aldactone Evaluation Study (RALES) did not report the effects of spironolactone (Aldactone®, Pfizer Ltd) on blood pressure [28].

Not all blood pressure-lowering drugs were efficacious in reducing cardiovascular events in patients with heart failure. Despite having lowered systolic and diastolic blood pressure by 2 mmHg, the benefits of amlodipine (Istin®, Pfizer Ltd) were restricted to patients with heart failure secondary to nonischemic cardiomyopathy [29]. The lack of efficacy in patients with ischemic heart disease may be related to the lower efficacy of calcium-channel blockers in the primary prevention of heart failure and coronary heart disease [30].

Most trials carried out on patients with diabetes, evidence of cardiovascular disease, and heart failure employed an ACE inhibitor as the active treatment. The blood pressure-lowering effect of these drugs was largely disregarded in the interpretation of most trials, and antiatherosclerotic and neurohumoral effects of ACE inhibition were postulated as the explanatory mechanisms for the beneficial effects. These interpretations should be reconsidered in view of the results of the ALLHAT trial [12]. In this landmark trial, hypertensive patients treated with lisinopril had a higher incidence of stroke, cardiovascular disease, heart failure, angina and coronary revascularization than those patients treated with chlorthalidone. The advantage of chlorthalidone could be ascribed to its higher blood pressure-lowering effect, and suggests that the postulated antatherosclerotic effects of the ACE inhibitors were not able to compensate for their less efficacious blood pressure-lowering effect. The absence of effect of perindopril alone in the PROGRESS trial strengthens this interpretation [16].

Since most trials have been carried out with ACE inhibitors, these drugs may generally be preferred for lowering blood pressure in normotensive individuals. A noticeable exception is the choice for patients who have recovered from a stroke, who should be treated with a combination of an ACE inhibitor and a diuretic.

In conclusion, the risks of increasing blood pressure demonstrated in observational studies, and of the results of several clinical trials, strongly support the interpretation that blood pressure-lowering drugs are essential for certain patients with normal blood pressure. Patients with Type 2 diabetes mellitus, heart failure (both symptomatic and nonsymptomatic), and any evidence of atherosclerotic disease in the coronary, cerebral, and peripheral territories, should be treated with one or two antihypertensive drugs. The possibility that a more intense reduction of blood pressure in some of these conditions could be beneficial should be explored in further clinical trials.

**Key issues**

- The risk of increasing blood pressure for the incidence of cardiovascular disease has been accurately estimated and starts at 115/75 mmHg.
- This risk doubles for every 10 year increase in age, 20 mmHg increase in systolic blood pressure, 10 mmHg increase in diastolic blood pressure, or in the presence of comorbidities, such as diabetes or any evidence of cardiovascular disease.
- More than half of coronary and cerebrovascular events can be explained by blood pressures of more than 115/75 mmHg.
- The benefit of further lowering blood pressure that is within the normal range has been demonstrated by randomized clinical trials in patients with diabetes, overt and nonovert heart failure, or with any evidence of atherosclerotic disease in the coronary, cerebral or peripheral territories.
- Angiotensin-converting enzyme inhibitors are the drugs that have been most tested in such conditions. In view of the recent results of the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) and Perindopril PROtection aGainst REcurrent Stroke Study (PROGRESS), it is likely that most of their benefits are derived from their blood pressure-lowering effect, rather than a primary antiatherosclerotic effect.
Expert opinion & five-year view

The threshold levels for normal blood pressure are derived from the concept of hypotension, in other words, blood pressure levels not able to perfuse tissues in a wide range of physiological conditions. Blood pressure values above these limits are associated with an increased cardiovascular risk. The magnitude of this risk is relevant in the presence of certain conditions, such as diabetes and any evidence of cardiovascular disease. The results of several clinical trials have shown the definite benefit for the use of blood pressure-lowering drugs in these conditions, independently of the diagnosis of hypertension, a denomination that should be avoided in the future. Because of their higher cardiovascular risk, healthier elderly individuals would probably benefit from the use of blood pressure-lowering drugs independent of their blood pressure levels, a hypothesis that may be explored in randomized clinical trials. Young individuals free of diabetes or cardiovascular disease should be encouraged to assume healthier habits in order to prevent blood pressure increasing with age.

References

Papers of special note have been highlighted as:
- of interest
- of considerable interest


3. This trial is one of the foundations of the modern medicine, demonstrating the strong benefit derived from the drug treatment of patients with severe hypertension.


11. Creative, systematic review of the evidence, demonstrating the close relationship between the intensity of blood pressure lowering and the reduction in the incidence of major cardiovascular events.


13. Landmark trial, which showed that diuretics (old and inexpensive antihypertensive drugs) are the most efficacious agents for starting the treatment of hypertension in a wide range of racial, age, and medical condition groups.


17. Results of this trial should be urgently incorporated into clinical practice; the use of a diuretic and an ACE inhibitor is the most efficacious approach to prevent a new stroke in patients who have recovered from a previous one.


One of several clinical trials that demonstrates the benefit of the use of angiotensin-converting enzyme inhibitors in patients with heart failure.


New approach to the evidence, showing the advantage of diuretics over other classes of blood pressure-lowering drugs in the prevention of various cardiovascular events.

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