Treatment options for hypertension in high-risk patients

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Abstract: Patients are considered to be at high risk of cardiovascular events if they have diabetes, chronic kidney disease, stroke, established coronary artery disease, or a coronary artery disease equivalent. Blood pressure-lowering therapy has been shown to reduce cardiovascular events in these patients significantly. Identification of high-risk patients by global risk evaluation is recommended for every hypertensive patient. Treatment of hypertension in high-risk patients with an angiotensin-converting enzyme inhibitor or an angiotensin receptor antagonist, with or without addition of a dihydropyridine calcium channel antagonist, is a reasonable approach based on current clinical trials.

Keywords: hypertension, high-risk, antihypertensive agent

Introduction
Cardiovascular disease is an important cause of death worldwide. Hypertension is one of the major risk factors and is correlated with a risk of stroke, coronary artery disease, peripheral vascular disease, heart failure, and renal disease. Together with other risk factors, including diabetes mellitus, dyslipidemia, smoking, and obesity, hypertension significantly contributes to the global cardiovascular burden of morbidity and mortality, as well as increasing individual absolute cardiovascular risk.

Identifying and treating risk factors in patients at high risk of cardiovascular events can significantly reduce the risk. Patients are considered to be at high risk if they have diabetes, chronic kidney disease, stroke, established coronary artery disease, or a coronary artery disease equivalent, including carotid artery disease, peripheral arterial disease, and abdominal aneurysm. Blood pressure-lowering therapy has been shown to reduce cardiovascular events in these patients significantly. Successful prevention of cardiovascular events in high-risk patients requires identification of patients at risk and comprehensive risk factor management, including treatment of hypertension.

Identification of high-risk patients
The risk of a cardiovascular event increases dramatically when a hypertensive patient has vascular disease, including coronary artery disease, cerebrovascular disease, and peripheral vascular disease. In patients with diabetes mellitus, up to 65% of deaths are due to coronary artery disease and/or stroke, and diabetes mellitus has been considered as a coronary disease equivalent. Clustering of risk factors increases the risk of cardiovascular events.

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Trial demonstrated that cardiovascular mortality increases significantly when the number of risk factors accumulates. The presence of left ventricular hypertrophy has also been shown to increase the risk of cardiovascular events in hypertension significantly.

Total cardiovascular risk assessment is recommended during the initial evaluation of all hypertensive patients. Factors influencing prognosis include blood pressure levels, other cardiovascular risk factors, diabetes mellitus or metabolic syndrome, subclinical organ damage, and established vascular or renal disease. A summary of high-risk conditions is listed in Table 1.

**Major trials in high-risk patients**

Many clinical trials have investigated the effects of reducing cardiovascular risk in the treatment of hypertension. These large, randomized, controlled trials provide clinical evidence and have implications for the treatment of hypertension in high-risk patients (Table 2).

The Heart Outcomes Prevention Evaluation study demonstrated that the angiotensin-converting enzyme inhibitor, ramipril, could significantly reduce primary endpoints (myocardial infarction, stroke, cardiovascular death) in high-risk patients. The Losartan Intervention For Endpoint reduction in hypertension study compared the angiotensin receptor antagonist, losartan, with the beta-blocker, atenolol, in patients with left ventricular hypertrophy. The degree of left ventricular hypertrophy regression and primary endpoints (myocardial infarction, stroke, cardiovascular death) were significantly improved in the losartan group than in the atenolol group. The Anglo-Scandinavian Cardiac Outcome Trial – Blood Pressure Lowering Arm compared amloidipine-based (with or without an angiotensin-converting enzyme inhibitor) and atenolol-based (with or without a thiazide diuretic) treatment in hypertensive patients with three or more study-specified risk factors. This study did not show any differences in the primary endpoints (nonfatal myocardial infarction and fatal coronary artery disease), but did show a significantly reduced number of overall cardiovascular events (hazard ratio [HR] 0.84, 95% confidence interval 0.78–0.90, P < 0.0001) in the amloidipine-based treatment group. The Action in Diabetes and Vascular Disease: Preterax and Diamicron-Controlled Evaluation Trial included patients with Type 2 diabetes mellitus and assessed the effects of the combination of the angiotensin-converting enzyme inhibitor, perindopril, and a diuretic, indapamide, on vascular events. The primary endpoints (macrovascular and microvascular events) were significantly reduced in the active treatment group (relative risk reduction 9%, P = 0.04). All cause mortality (HR 0.86, P = 0.03) and coronary events (HR 0.86, P = 0.02) were also significantly reduced in the active treatment group. The Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) study involved high-risk patients with coronary, peripheral arterial, or cerebrovascular disease, and diabetic patients with target organ damage. The patients were randomized into ramipril, telmisartan, and ramipril + telmisartan groups. The primary endpoints (the composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure) were similar in these groups. However, more hypotension and renal dysfunction were noted in the combination group. The Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease study included patients who were screened for the ONTARGET study but were unable to tolerate angiotensin-converting enzyme inhibitors. The primary composite outcome was the same as for the ONTARGET study, and occurred in 15.7% of the telmisartan patients and 17.0% of the placebo patients (P = 0.22). However, the telmisartan group had significantly lower composite secondary outcomes (P = 0.048). The Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension study tested whether treatment with the combination of an angiotensin-converting enzyme inhibitor and a dihydropyridine calcium channel blocker was more effective than combination with a thiazide in cardiovascular event reduction. The primary outcome (the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization) was significantly lower in the benazepril + amloidipine group than in the benazepril + hydrochlorothiazide group.

### Table 1: High risk conditions in hypertension

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
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<tbody>
<tr>
<td>Systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 110 mmHg</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Metabolic syndrome</td>
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<tr>
<td>Three or more cardiovascular risk factors</td>
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<tr>
<td>One or more manifestations of subclinical organ damage, eg, left ventricular hypertrophy</td>
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<tr>
<td>Established coronary artery disease</td>
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<tr>
<td>Established cerebrovascular disease</td>
<td></td>
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<tr>
<td>Established peripheral vascular disease</td>
<td></td>
</tr>
<tr>
<td>Established chronic kidney disease</td>
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</tbody>
</table>

**Note:** Adapted from the 2007 European Society of Hypertension and the European Society of Cardiology guidelines for the treatment of arterial hypertension.
Table 2  Major clinical trials on the treatment of hypertension for high-risk patients

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Patients randomized (n)</th>
<th>Characteristics of study population</th>
<th>Drugs</th>
<th>Duration (years)</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Outcomes Prevention Evaluation (HOPE)</td>
<td>9541</td>
<td>Age ≥55 years with one high-risk condition</td>
<td>Ramipril Placebo</td>
<td>4.5</td>
<td>Ramipril 14.0% versus placebo 17.6% (P &lt; 0.001)</td>
</tr>
<tr>
<td>Losartan Intervention For Endpoint reduction in hypertension (LIFE)</td>
<td>9193</td>
<td>Hypertension and left ventricular hypertrophy</td>
<td>Losartan Atenolol</td>
<td>4.8</td>
<td>Losartan 11.0% versus atenolol 12.8% (P = 0.021)</td>
</tr>
<tr>
<td>Anglo-Scandinavian Cardiac Outcome Trial (ASCOT) blood-pressure-lowering arm</td>
<td>19,257</td>
<td>Hypertension with ≥3 specified risk factors</td>
<td>Amlodipine ± perindopril Atenolol ± bendrofluromethiazide-K</td>
<td>5.0</td>
<td>Perindopril + indapamide 15.5% versus placebo 16.8% (P = 0.04)</td>
</tr>
<tr>
<td>Action in Diabetes and Vascular Disease: Preterax and Diamicron-Controlled Evaluation Trial (ADVANCE)</td>
<td>11,140</td>
<td>Diabetes mellitus</td>
<td>Placebo</td>
<td>4.3</td>
<td>Placebo</td>
</tr>
<tr>
<td>Ongoing Telmisartan alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET)</td>
<td>25,620</td>
<td>High-risk patients with coronary, peripheral arterial, or cerebrovascular disease, or diabetic patients with target organ damage</td>
<td>Telmisartan + indapamide Placebo</td>
<td>4.7</td>
<td>Telmisartan 15.7% versus placebo 17.0% (P = 0.22)</td>
</tr>
<tr>
<td>Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND)</td>
<td>6666</td>
<td>As ONTARGET study with angiotensin-converting enzyme inhibitor intolerance</td>
<td>Atenolol</td>
<td>4.7</td>
<td>Atenolol</td>
</tr>
<tr>
<td>Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLiSH)</td>
<td>11,506</td>
<td>High-risk hypertensive patients</td>
<td>Benazepril + amlodipine Benazepril + hydrochlorothiazide</td>
<td>3.0</td>
<td>Benazepril + amlodipine 9.6% versus benazepril + hydrochlorothiazide 11.6% (P &lt; 0.001)</td>
</tr>
</tbody>
</table>

From the results of these trials, it is reasonable to recommend using an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for the treatment of hypertension in high-risk patients. The combination of an angiotensin-converting enzyme inhibitor with an angiotensin receptor blocker was also shown to be beneficial in the treatment of high-risk patients. However, the combination of an angiotensin-converting enzyme inhibitor with angiotensin receptor blocker should only be used sparingly and very carefully in patients at high risk based on the currently available evidence.16

Level and speed of blood pressure-lowering in high-risk patients

Most of the hypertension treatment guidelines recommend a blood pressure target of <130/80 mmHg for high-risk patients. However, the combination of an angiotensin-converting enzyme inhibitor with angiotensin receptor blocker was also shown to be beneficial in the treatment of high-risk patients. Therefore, the combination of an angiotensin-converting enzyme inhibitor with angiotensin receptor blocker should only be used sparingly and very carefully in patients at high risk based on the currently available evidence.
effects of blocking the renin-angiotensin-aldosterone system by angiotensin-converting enzyme inhibitors or angiotensin-
receptor blockers in high-risk patients, direct renin inhibitors
have attracted interest due to their protective effects in
high-risk patients. Direct renin inhibitors block the renin-
angiotensin-aldosterone system at its point of origin, and it
decrease plasma renin activity by blocking renin or prorenin
receptors and eliminating the adverse effects of renin or prorenin receptor activation. Some studies of organ
protective effects have shown comparative or even better
results with angiotensin-converting enzyme inhibitors or
angiotensin receptor blockers when a direct renin inhibitor
was used as monotherapy or in combination with other
renin-angiotensin-aldosterone system inhibitors. The organ
protective effect of direct renin inhibitors has been shown
to be more pronounced for the kidney. Direct renin inhibitors
showed a good and rapid blood pressure-lowering response
when used in combination with a calcium channel antagonist
in a recently published hypertension study. Used alone or in
combination, direct renin inhibitors have great potential in
the treatment of hypertension in high-risk patients. However,
results of large randomized controlled studies for the major
cardiovascular endpoints are needed to define their role in
high-risk patients.

Conclusion
Treatment of hypertension in high-risk patients can reduce cardiovascular events. Identification of high-risk patients by global risk evaluation is recommended for every hypertensive patient. Treatment of hypertension in high-risk patients with an angiotensin-converting enzyme inhibitor or an angiotensin receptor antagonist, with or without addition of a dihydropyridine calcium channel blocker, is a reasonable approach based on current clinical trial evidence.

Disclosure
The author reports no conflict of interest in this work.

References

