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REVIEW

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.[1,2] 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.[3]

Identifying and treating risk factors in patients at high risk of cardiovascular events can significantly reduce the risk.[4] 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.[1] Blood pressure-lowering therapy has been shown to reduce cardiovascular events in these patients significantly.[5] Successful prevention of cardiovascular events in high-risk patients requires identification of patients at risk and comprehensive risk factor management, including treatment of hypertension.

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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.[1,4,6] 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.[4,7] Clustering of risk factors increases the risk of cardiovascular events. The Multiple Risk Factor Intervention

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Trial demonstrated that cardiovascular mortality increases significantly when the number of risk factors accumulates.[8] The presence of left ventricular hypertrophy has also been shown to increase the risk of cardiovascular events in hypertension significantly.[9]

Total cardiovascular risk assessment is recommended during the initial evaluation of all hypertensive patients.[10] 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.[10] 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).[11–17]

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.[11] 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.[12] The Anglo-Scandinavian Cardiac Outcome Trial – Blood Pressure Lowering Arm compared amlodipine-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 amlodipine-based treatment group.[13] 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.[14] 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.[15] 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 ($P = 0.048$).[16] 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 + amlodipine group than in the benazepril + hydrochlorothiazide group.[17]

Table 1 High risk conditions in hypertension*

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

Note: *Adapted from the 2007 European Society of Hypertension and the European Society of Cardiology guidelines for the treatment of arterial hypertension.[10]

Table 2 Major clinical trials on the treatment of hypertension for high-risk patients

Trial name	Patients randomized (n)	Characteristics of study population	Drugs	Duration (years)	Primary endpoint
Heart Outcomes Prevention Evaluation (HOPE)[11]	9541	Age ≥55 years with one high-risk condition	Ramipril Placebo	4.5	Ramipril 14.0% versus placebo 17.8% ($P < 0.001$)
Losartan Intervention For Endpoint reduction in hypertension (LIFE)[12]	9193	Hypertension and left ventricular hypertrophy	Losartan Atenolol	4.8	Losartan 11.0% versus atenolol 12.8% ($P = 0.021$)
Anglo-Scandinavian Cardiac Outcome Trial (ASCOT) blood pressure-lowering arm[13]	19,257	Hypertension with ≥3 specified risk factors	Amlodipine ± perindopril Atenolol ± bendroflumethiazide-K	5.0	Amlodipine-based 4.5% versus atenolol-based 4.9% ($P = 0.105$)
Action in Diabetes and Vascular Disease: Preterax and Diamicron-Controlled Evaluation Trial (ADVANCE)[14]	11,140	Diabetes mellitus	Perindopril + indapamide Placebo	4.3	Perindopril + indapamide 15.5% versus placebo 16.8% ($P = 0.04$)
Ongoing Telmisartan alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET)[15]	25,620	High-risk patients with coronary, peripheral arterial, or cerebrovascular disease, or diabetic patients with target organ damage	Ramipril Telmisartan Ramipril + telmisartan	4.7	Ramipril 16.5% versus telmisartan 16.7% versus ramipril + telmisartan 16.3%
Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND)[16]	6666	As ONTARGET study with angiotensin-converting enzyme inhibitor intolerance	Telmisartan Placebo	4.7	Telmisartan 15.7% versus placebo 17.0% ($P = 0.22$)
Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH)[17]	11,506	High-risk hypertensive patients	Benazepril + amlodipine Benazepril + hydrochlorothiazide	3.0	Benazepril + amlodipine 9.6% versus benazepril + hydrochlorothiazide 11.6% ($P < 0.001$)

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 or angiotensin receptor blocker with a dihydropyridine calcium channel blocker was also shown to be beneficial in the treatment of high-risk patients. However, the combination of an angiotensin-converting enzyme inhibitor with an angiotensin receptor blocker should only be used sparingly and very carefully in patients at high risk based on the currently available evidence.[18]

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.[1,9,10] Critical analyses of the results of available trials show that the evidence is scanty for this recommendation.[19] Most of the clinical trials did not reach this blood pressure target when treating-high risk patients, and the recommendation is based more on assumptions than on hard evidence.[19] The Action to Control Cardiovascular Risk in Diabetes blood pressure trial demonstrated that targeting a systolic blood pressure of <120 mmHg as compared with <140 mmHg did not reduce cardiovascular risk in high-risk diabetes patients.[20] Further studies are needed to confirm the ideal blood pressure target for high-risk patients. Nonetheless, all observations indicate that aiming at a lower blood pressure target of 130 mmHg does not increase risk and is well tolerated.[19] Therefore, it is acceptable currently to advise targeting a systolic blood pressure of 130 mmHg in clinical practice.

There is no doubt that antihypertensive medication should be initiated immediately in high or very high-risk hypertensive patients.[10] The concept of "sooner is better" is important for high-risk patients based on the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial.[21] The VALUE trial showed that a greater blood pressure reduction in the first six months in the amlodipine group was associated with a lower cardiovascular event rate than in the valsartan group.[21]

Role of direct renin inhibitors in high-risk patients

The direct renin inhibitor, aliskiren, has recently been developed for the treatment of hypertension. Based on the successful results of previous studies regarding the protective

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 also decrease plasma renin activity by blocking renin or prorenin receptors and eliminating the adverse effects of renin or prorenin receptor activation.[22] 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.[23] The organ protective effect of direct renin inhibitors has been shown to be more pronounced for the kidney.[24] 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.[25] 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.

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