Aggressive blood pressure control and stroke prevention: role of calcium channel blockers

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Cerebrovascular disease is a major cause of morbidity and mortality worldwide and its prevalence is expected to increase as a result of projected demographic trends. Stroke is one of the leading causes of disability and death of over 30 million people each year worldwide. Hypertension is the most important modifiable risk factor for stroke. Recent data indicate that treatment with antihypertensive drugs reduces the incidence of all strokes in men (by 34%), women (by 38%), the elderly (by 36%), including those older than 80 years (by 34%), younger persons, those with systolic and diastolic hypertension, persons with isolated systolic hypertension, and those with a history of stroke or transient ischemic attack (by 28%). Furthermore, several large, prospective, randomized, clinical outcome trials have shown that calcium channel blockers (CCBs) are effective and safe antihypertensive drugs compared with placebo and reduce the cardiovascular morbidity and mortality of treated patients. Moreover, when CCBs were compared with conventional antihypertensive drugs they demonstrated similar blood pressure-lowering effects and similar reductions in cardiovascular morbidity and mortality, with the exception of a higher incidence of heart failure and fatal myocardial infarction in some studies. Considering all the evidence available today, however, these drugs should be considered safe for the treatment of the uncomplicated hypertensive patient in combination with other drugs. They can also be used as first-line therapy for older, stroke-prone hypertensive patients. The aim of this review is to summarize the role of CCBs in the prevention of stroke.

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Abbreviations: CCbs, Calcium channel blockers; ACEI, Angiotensin-Converting Enzyme Inhibitors; VHAS, Verapamil in Hypertension and Atherosclerosis Study; ELSA, European Lacidipine Study on Atherosclerosis; INSIGHT, Intervention as a Goal in Hypertension Treatment; Syst-Eur, Systolic Hypertension in Europe; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; NORDIL, Nordic Diltiazem; Syst-China, Systolic Hypertension in China; STOP-Hypertension-2, Swedish Trial in Old Patients with Hypertension; FEVER, Felodipine Event Reduction; MOSES, Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention; LIFE, Losartan Intervention For Endpoint reduction in hypertension; SCOPE, Study on COgnition and Prognosis in the Elderly; VALUE, Valsartan Antihypertensive Long-term Use Evaluation; HOPE, Heart Outcomes Prevention Evaluation; PROGRESS, Perindopril protection against recurrent stroke study; CAPPP, Captopril Prevention Project; ARBs, Angiotensin receptor blockers; ACCOMPLISH, Avoiding Cardiovascular Events through Combination therapy in Patients living with Systolic Hypertension

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Introduction

Cerebrovascular disease is a major cause of morbidity and mortality worldwide, and its prevalence is expected to increase as a result of projected demographic trends. Stroke is estimated to be responsible for 5.1 million of the 16.7 million cardiovascular disease deaths that occur every year worldwide, making it the second leading cause of death [1,2]. Two-thirds of the deaths occur among people living in developing countries [3]. In addition, many survivors of stroke have to adjust to a life with varying degrees of disabilities. The treatment of stroke is associated with extremely high costs, with more than US$49 billion spent on stroke-related illnesses in the United States in 2002 [4].

Causes of stroke: role of hypertension

The main causes of stroke are atherothromboembolism and cardiogenic embolism. The main causal and treatable risk factors for atherothromboembolic ischemic stroke are increasing blood pressure (BP), increasing cholesterol, cigarette smoking, and diabetes; and the main risk factors for cardiogenic ischemic stroke are atrial fibrillation and ischemic heart disease [5].

Hypertension is the most important modifiable risk factor for stroke. Recent surveys indicate that at least 65 million adults in the Unites States are diagnosed with hypertension, a 30% increase from 50 million in the last decade [6,7], whereas over 70% of strokes can be attributed to hypertension [8–10]. Aggressive antihypertensive therapy has been proven highly effective in reducing the risk of stroke. A recent published overview from a review of major overviews of prospective cohort studies and an updated meta-analysis of more than 40 randomized, controlled trials of BP lowering, which included more than 188 000 participants and approximately 6800 stroke events, has shown that epidemiologically expected benefits of BP lowering for stroke risk reduction are

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broadly consistent across a range of different population subgroups [11]. Particularly, evidence from large clinical trials indicate that treatment with antihypertensive drugs, keeping BP to less than 140/90 mmHg, reduces the incidence of all strokes in men by 34%, in women by 38%, in the elderly by 36%, including those older than 80 years by 34%, younger persons, those with diastolic hypertension by 34%, and in those with a history of stroke or transient ischemic attack by 28% [12,13].

Role of calcium channel blockers

Calcium channel blockers (CCBs) constitute a class of structurally heterogeneous drugs. Although all agents in this class work by blocking calcium channels, each subclass binds at a unique location [14,15]. Dihydropyridines include amlodipine, felodipine, nicardipine, and nifedipine, whereas nondihydropyridines comprise agents such as diltiazem and verapamil. Their structural heterogeneity leads to functional heterogeneity, particularly with regard to their vasodilator potency and ionotropic, chronotropic, and dromotropic effects on the heart (Table 1). Short-acting CCBs lead to a reflex neurohormonal activation of the sympathetic nervous system [16,17], characterized by tachycardia, increased cardiac output, and increased plasma catecholamine and plasma renin activity. These effects of the short-acting CCBs have been implicated in worsening cardiac events. Short-acting CCBs are no longer recommended for the long-term treatment of patients with hypertension or cardiovascular disease, particularly in the absence of β-blockade.

Calcium antagonists were introduced for the treatment of hypertension in the 1980s, lowering BP mainly through vasodilation and reduction of peripheral resistance. The most common side effects of these agents are peripheral edema, flushing, and headache [18–20]. A recent meta-analysis comparing the various drug classes with placebo or no-treatment showed that strokes were reduced with diuretics by 34%, with β-blockers by 29%, with angiotensin-converting enzyme inhibitors (ACEI) by 31%, and with CCBs by 40% [21]. From this meta-analysis, it seems that a CCBs-based regimen is superior to other regimens in preventing stroke.

The aim of this paper is to emphasize the importance of effective management of stroke risk factors, particularly hypertension, and to highlight the role of CCBs. Data were collected using MEDLINE searches, journal reviews, and original papers published till October 2007.

Table 1 Vasodilator potency and ionotropic, chronotropic, and dromotropic effects on the heart of calcium channel blockers

	Amlodipine	Diltiazem	Nifedipine	Verapamil
Heart rate	↑/0	↓	↓	↓
Sinoatrial node conduction	0	↓↓	0	↓
A trioventricular node conduction	0	↓	0	↓
Myocardial contractility	↓/0	↓	↓/0	↓↓
Neurohormonal activation	↑/0	↑	↑	↑
Vascular dilatation	↑↑	↑	↑↑	↑
Coronary flow	↑	↑	↑	↑

↓, decrease; 0, no change; ↑, increase.

Therapy of stroke

Introduction

Strategies to reduce the incidence of stroke include prevention of first and recurrent stroke and treatment of patients with acute stroke to reduce death and disability. The two main strategies of stroke prevention are the 'population' (or 'mass') approach and the 'high-risk' approach. The 'population' approach aims to reduce stroke by lowering the prevalence and mean level of causal risk factors in the community by means of public education and government legislation. The 'high-risk' approach aims to reduce stroke by identifying individuals at high risk of stroke and lowering their risk by means of optimal medical therapies [22]. Level 1 evidence from randomized, controlled trials indicates that effective treatments for high-risk patients include BP control [6–13], cholesterol reduction [23,24], glucose control [25], and leisure time physical activity [26].

Role of statins

The positive effect of statins on stroke have been discussed in meta-analysis that includes more than 90 000 patients of all randomized trials testing statin drugs published before August 2003. The results of primary prevention statin trials have shown a nonsignificant 9% reduction in fatal and nonfatal strokes {odds ratio (OR): 0.91 [95% confidence interval (CI): 0.76–1.10]}, whereas no increase was observed in hemorrhagic strokes [OR: 0.90 (95% CI: 0.65–1.22)]. Secondary stroke reduction was 27% ($P < 0.001$). The magnitude of stroke reduction was related to low-density lipoprotein cholesterol (LDL-C) reduction [10% reduction in LDL-C was estimated to reduce the risk of all strokes by 15.6% (95% CI: 6.7–23.6)], whereas other data suggest that other mechanisms could be involved independently of LDL-C reduction [27,28].

Role of warfarin or antiplatelet agents in carotid endarterectomy

The management of other risk factors of stroke, such as atrial fibrillation, with the use of pharmacological agents such as warfarin or antiplatelet agents cannot be overemphasized. Warfarin can reduce the risk of stoke by more than 60%, but effective therapy of A-fibrilation accounts for only 12% of stroke prevention. Indeed, a meta-analysis of 16 trials that included a total of 9874 participants (mean follow-up, 1.7 years) regarding the management of atrial fibrillation demonstrated that warfarin (six trials, 2900 participants) reduced stroke by 62% (95% CI: 48–72%), whereas the absolute risk reductions were 2.7% per year for primary stroke prevention and 8.4% per year for secondary stroke prevention [29].

Beyond risk factor reduction, antiplatelet therapy is an effective option for lowering the likelihood of stroke of patients at risk. Aspirin has been shown to be effective in the primary stroke prevention in women without affecting the risk of myocardial infarction or death from cardiovascular causes [30], whereas clinical studies provide little evidence that clopidogrel, with or without aspirin, is more effective in the secondary stroke prevention setting than aspirin alone [31,32]. Carotid endarterectomy should be considered for stroke prevention in patients with ischemic symptoms; for patients with asymptomatic stenosis, potential benefit must be balanced against surgical risk [33–35].

Role of antihypertensive agents

The above data indicate that effective management of risk factors is the key for stroke prevention. In particular, effective antihypertensive therapy seems to be the most important intervention because of not only BP reduction but also properties of individual antihypertensive agents.

Calcium channel blockers

Indeed, CCBs, especially the highly lipophilic amlodipine, lacidipine, and nisoldipine, have been shown to possess antioxidant properties. These drugs reduce the oxidation of LDL and its influx into the arterial wall and reduce atherosclerotic lesions in animals. Platelet production of malondialdehyde, a marker of oxygen free radical formation, is suppressed by amlodipine, lacidipine, or nifedipine in hypertensive patients [36].

In certain populations, CCBs may prevent the progression of carotid atherosclerosis, which is another possible mechanism independent of the BP that may contribute to stroke prevention. In 1998, CCBs was shown to reduce or prevent progression of the carotid intima–media thickness (IMT). Results from the small Verapamil in Hypertension and Atherosclerosis Study have shown that verapamil was more effective than chlorothalidone in promoting regression of thicker carotid lesions. Among the 456 patients with satisfactory baseline ultrasound readings, 33% were classified with normal carotid arteries, 27% with thickened carotid arteries, and 40% with plaques. The BP-lowering effect of the two randomized treatments was similar. Changes in the carotid IMT were small in both groups (0.015 mm per year) and the differences between the changes under the two treatments were consequently small (verapamil −0.082 vs. chlorothalidone −0.037 mm per year; $P < 0.02$), but the observation that these small differences in carotid wall changes were paralleled by differences in the incidence of cardiovascular events [19 events in the verapamil group and 35 in the chlorothalidone group, with a significantly ($P < 0.01$) greater incidence in patients with plaques and among patients with plaques in those who were randomized to chlorothalidone ($P < 0.05$)] suggests that even small effects on carotid plaques may have clinical and prognostic relevance [37].

Results from the European Lacidipine Study on Atherosclerosis suggest that CCBs may have favorable effects on carotid IMTs progression. Among 2334 patients with hypertension randomized to either lacidipine-based or atenolol-based regimens, the effects on an index of carotid atherosclerosis, the mean of the maximum IMTs in far walls of common carotids and bifurcations, CBM(max), were compared over a 4-year period. This index has been shown by epidemiological studies to be predictive of cardiovascular events. The effect of lacidipine was found to be significantly better ($P < 0.0001$) than that of atenolol, with a treatment difference in 4-year CBM(max) progression of −0.0227 mm (intention-to-treat population) and −0.0281 mm (completers). The yearly IMT progression rate was 0.0145 mm per year in atenolol-treated and 0.0087 mm per year in lacidipine-treated patients (completers: 40% reduction; $P = 0.0073$). These results are in agreement with the results from the International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) study, that also showed that, compared with coamilozide, nifedipine GITS was significantly more effective in preventing an increase in IMT in the carotid arteries [38,39]. Other clinical data from the double-blind, placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial have previously shown a 55% reduction in the incidence of dementia after a median follow-up of 2.0 years [(from 7.4 to 3.3 patients per 1000 patient-years (43 vs. 21 patients; $P < 0.001$)]. After adjusting for sex, age, education, and entry BP, the relative hazard rate associated with the use of nitrendipine was 0.38 (95% CI: 0.23–0.64; $P < 0.001$). Treatment of 1000 patients for 5 years can prevent dementia in 20 patients (95% CI: 7–33) [40]. Prevention of stroke by mechanisms other than BP control may partially contribute to dementia prevention.

Numerous comparative clinical trials and meta-analyses indicate that CCBs may be useful as a first-line treatment in the prevention of stroke. The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the largest and most important BP trial ever done in the United States [41], was a randomized, double-blind, active-controlled clinical trial with 33 357 hypertensive patients randomized to receive chlorothalidone ($n = 15\,255$), amlodipine ($n = 9048$), or lisinopril ($n = 9054$) for planned follow-up of approximately 4–8 years. The primary outcome was a composite of fatal coronary heart disease and nonfatal myocardial infarction. Secondary outcomes comprised all-cause mortality, stroke, and other cardiovascular disease events. No significant difference was observed between the amlodipine and chlorothalidone groups with regards to the primary outcome (relative risk [RR] 0.98; 95% CI: 0.90–1.07), as well as the secondary outcomes, except for a higher 6-year

Table 2

Study	Patients population	Number of patients	Treatment of groups	Incidence of stroke
ALLHAT	Hypertensive patients	24 309	Lisinoplil vs. chlorothalidone	15% increase
NORDIL	Hypertensive patients	10 881	Diltiazem vs. diuretics and β-blockers	25% decrease
INSIGHT	Hypertensive patients	6 321	Nifedipine vs. coamilozide	10% decrease
Syst-Eur-ISH	Elderly hypertensive patients	4 695	Immediate vs. delayed therapy	28% decrease
Syst-China-ISH	Elderly hypertensive patients	1 253	Active treatment	38% decrease
STOP-2	Elderly hypertensive patients	6 614	Newer vs. old drugs	25% decrease
ASCOT-BPLA	Hypertensive patients	19 257	Perin. + Amlod. vs. Aten. + Hydroch.	23% decrease
FEVER	Hypertensive patients	9 800	Hydroch. + Felod vs. Hydroch.	27% decrease
MOSES	Poststroke hypertensive patients	1 405	Eprosartan vs. nitredipine	25% decrease

Amlod., amlodipine; Aten., atenolol; Felod., felodipine; Hydroch., hydrochlorothiazide; Perin., perindopril.

incidence of heart failure with amlodipine (10.2 vs. 7.7%; RR 1.38; 95% CI: 1.25–1.52). Particularly, patients treated with amlodipine had lower risk of stroke compared with those treated with chlorothalidone (RR 0.93; 95% CI: 0.82–1,06), although the difference was not statistically significant. Notice that the observation that the differences between the treatment groups regarding the stroke were observed as early as 6 months after treatment initiation [42]. In the same study, lisinopril had a higher 6-year rate of stroke compared with chlorothalidone (6.3 vs. 5.6%; RR 1.15; 95% CI: 1.02–1.30) [43]. In African–Americans, both diuretics and CCBs did better than ACE inhibition in stroke prevention. Some, or most, of the benefits could be attributed to BP difference [44,45]. Although ALLHAT concluded that thiazide-type diuretics are the preferred first-line antihypertensive therapy in hypertensive patients at high risk of stroke, dihydropyridines offer similar prevention except for heart failure (Table 2).

The Nordic Diltiazem (NORDIL) and the INSIGHT studies were the first two randomized interventional trials in hypertensive patients that directly compared the effects of therapy based on CCBs with those of diuretic and β-blocker-based treatment on major cardiovascular end points. Particularly, the NORDIL study was a prospective, randomized, open, blinded end point study, with 10 881 patients randomized to diltiazem, or diuretics, β-blockers, or both regimens, respectively, whereas the INSIGHT was a prospective, randomized, double-blind trial with 6321 patients randomized equally to receive nifedipine or coamilozide (hydrochlorothiazide and amiloride).

The two studies shared several nonsignificant trends for cause-specific events, including greater stroke prevention and lesser coronary event prevention in the CCB groups compared with the diuretic and β-blocker groups. Particularly in the NORDIL study, the diltiazem regimen was found to be more effective than the diuretic or β-blocker in lowering the rate of fatal and nonfatal stroke [6.4 vs. 9 events per 1000 patient-years; 0.80 (0.65–0.99); $P = 0.04$]; however, the INSIGHT study showed a trend toward nonsignificant reduction in strokes in the nifedipine-based regimen compared with coamilozide-based regimen [46–50].

Other beneficial effect in the prevention of stroke with the use of CCBs has been observed in patients with isolated systolic hypertension. The Syst-Eur trial assesses the impact of immediate vs. delayed antihypertensive treatment on the outcomes of 4695 older patients with isolated systolic hypertension. Immediate treatment prevented 17 strokes or 25 major cardiovascular events per 1000 patients compared with delayed treatment, reducing the occurrence of stroke and cardiovascular complications by 28% ($P = 0.01$) and 15% ($P = 0.03$), respectively [51].

Similar results were obtained by the Systolic Hypertension in China (Syst-China) Collaborative Group who investigated whether active treatment (nitrendipine, with the possible addition of captopril, and/or hydrochlorothiazide) could reduce the incidence of stroke and other cardiovascular complications in 1253 Chinese older patients with isolated systolic hypertension. The results have shown that active treatment reduces total strokes by 38% (from 20.8 to 13.0 end points per 1000 patient-years; $P = 0.01$) and stroke mortality by 58% (from 6.9 to 2.9 end points per 1000 patient-years; $P = 0.02$) [52,53]. The last two studies were placebo controlled and some, if not all, of the benefits could be attributed to BP reduction. Nevertheless, stroke prevention was impressive in the groups that received CCB therapy.

Finally, the results of a subgroup analysis of the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension-2) study on 6614 elderly patients with isolated systolic hypertension randomized to one of the three treatment groups, 'conventional' antihypertensive therapy with β-blockers or diuretics (atenolol, metoprolol, pindolol, or fixed-ratio hydrochlorothiazide and amiloride), ACEI (enalapril or lisinopril), or CCBs (felodipine or isradipine), have demonstrated that all stroke events, that is, fatal and nonfatal stroke together, were significantly reduced by 25% in the newer-drugs group (ACEI and CCBs) than in the β-blockers or diuretics conventional group (95% CI: 0.58–0.97; $P = 0.027$). This difference

was attributable to reduction in nonfatal stroke, whereas fatal stroke events did not differ between the groups [54].

The Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) compares the effect of atenolol with a thiazide diuretic with amlodipine with perindopril on cardiovascular events. Nineteen thousand, two hundred and fifty-seven patients were assigned to amlodipine and perindopril as required, or atenolol, adding bendroflumethiazide, and potassium as required. The amlodipine-based regimen had statistically significant fewer fatal and nonfatal stroke (327 vs. 422; 0.77; 0.66–0.89; $P = 0.0003$) compared with the atenolol-based regimen [55]. Again in this study, a small difference in BP could explain some of the differences in outcomes. Similar results were obtained by the Felodipine Event Reduction trial designed to compare the incidence of stroke and other cardiovascular events in 9800 Chinese hypertensive patients receiving a low-dose diuretic and low-dose calcium antagonist (felodipine) combination with those receiving low-dose diuretic as monotherapy. The results of the follow-up of these patients at 3-month intervals for an average of 40 months have shown that fatal and nonfatal strokes in the felodipine group were statistically significantly reduced by 27% ($P = 0.001$) [56].

Angiotensin receptor blockers

Angiotensin receptor blockers (ARBs) also seem to be effective agents in preventing stroke, perhaps possessing properties that prevent stroke beyond their effect on BP. In the Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention study, the AT1 receptor blocker eprosartan was compared with the CCB nitrendipine in the secondary prevention of stroke. Eprosartan was found to be more effective than nitrendipine for the same level of BP control in reducing cerebrovascular (IDR: 0.75; 95% CI: 0.58–0.97; $P = 0.03$) and cardiovascular (IDR: 0.75; 95% CI: 0.55–1.02; $P = 0.06$) events in patients with a history of prior stroke [57].

Similar results were obtained with other ARBs. The Losartan Intervention For Endpoint reduction in hypertension study, which included 9193 patients with hypertension and left ventricular hypertrophy randomized equally to an atenolol-based regimen and to a losartan-based regimen, demonstrates a 25% fewer fatal and nonfatal strokes (IDR: 0.75; 95% CI: 0.63–0.89; $P = 0.001$) [58] in patients randomized to the losartan-based regimen. Beneficial effects were also shown with candesartan in the Study on Cognition and Prognosis in the Elderly. In this study, patients were equally randomized to receive standard therapy alone or in addition with candesartan. Nonfatal stroke was reduced by 28% ($P = 0.04$) in the candesartan group than in the control group [59].

The Valsartan Antihypertensive Long-term Use Evaluation study compared the angiotensin II antagonist (valsartan) with amlodipine in a high-risk hypertensive population. The main hypothesis of the Valsartan Antihypertensive Long-term Use Evaluation trial was that, for an equivalent decrease in BP, valsartan would be more effective than amlodipine in decreasing cardiac mortality and morbidity [60,61]. BP was reduced by both treatments, but the effects of the amlodipine-based regimen were more pronounced, especially in the early period (BP difference of 4.0/2.1 mmHg lower in amlodipine than in valsartan group after 1 month; 1.5/1.3 mmHg after 1 year; $P < 0.001$ between groups). The primary composite end point occurred in 810 patients in the valsartan group (10.6%, 25.5 per 1000 patient-years) and 789 in the amlodipine group (10.4%, 24.7 per 1000 patient-years; hazard ratio 1.04; 95% CI: 0.94–1.15; $P = 0.49$) [62,63]. Stroke incidence was nonsignificantly and myocardial infarction was significantly lower in the amlodipine-based regimen, whereas cardiac failure was nonsignificantly lower in the valsartan group [64,65].

Angiotensin-converting enzyme inhibitors

The Heart Outcomes Prevention Evaluation Study investigators randomized 9297 high-risk patients to receive ramipril or matching placebo for a mean of 5 years. Results showed that treatment with ramipril reduced the rates of stroke (3.4 vs. 4.9%; RR 0.68; $P < 0.001$) [66]. The BP reduction, however, could explain most of the results. Several other studies that utilized ACEI compared with placebo or other therapies came out with less impressive results.

The Perindopril Protection Against Recurrent Stroke Study reduced the risk of stroke among 6105 hypertensive and nonhypertensive individuals with a history of stroke or transient ischemic attack only in combination with indapamide (14% reduction with perindopril alone vs. 43% in combination with indapamide). Recent data from the same trial have shown that during a mean of 3.9 years of follow-up, active treatment (perindopril for all participants and indapamide for those with neither an indication for nor a contraindication to a diuretic) reduced the absolute rates of ischemic stroke from 10 to 8% [relative risk reduction (RRR): 20%; 95% CI: 10–35] and the absolute rates of intracerebral hemorrhage from 2 to 1% (RRR: 50%; 95% CI: 26–67). The RR of any stroke during follow-up was reduced by 26% (95% CI: 12–38) among patients whose baseline cerebrovascular event was an ischemic stroke and by 49% (95% CI: 18–68) among those whose baseline event was an intracerebral hemorrhage [67,68].

The Captopril Prevention Project, a randomized trial, compared the effects of ACEI captopril with that of conventional therapy (diuretics and β-blockers) on cardiovascular morbidity and mortality in 10 985 patients

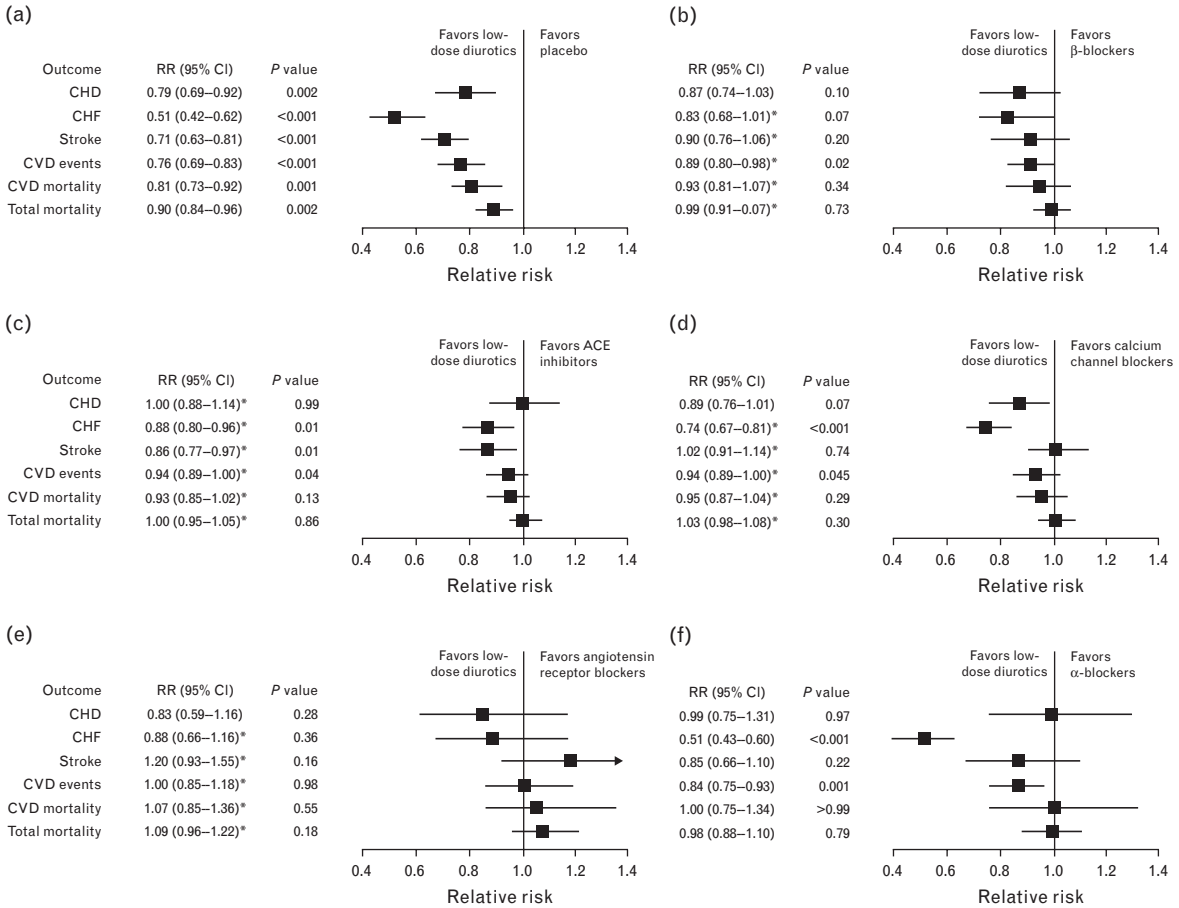
with hypertension. Fatal and nonfatal stroke were more common with captopril [189 vs. 148; 1.25 (1–01–1–55); $P = 0.044$] [69]. The difference in stroke risk was attributed to higher pressures in patients randomized to the captopril group. The ALLHAT study demonstrated a 15% higher incidence of strokes in the lisinopril group overall and a 40% higher incidence of strokes in black patients compared with the chlorothalidone group [43].

Recent meta-analysis on stroke outcomes with calcium channel blockers

A recently published meta-analysis of CCB trials used in the prevention of stroke demonstrated that CCBs reduced the risk of stroke more effectively than the other treatments in patients with essential hypertension. In 2002, Opie and Schall [70] analyzed the data of six clinical trials and reported that CCBs were associated with a lower risk of nonfatal stroke by 16% ($P = 0.013$). The above analysis did not include the ALLHAT trial, which was incorporated into a subsequent meta-analysis.

Staessen *et al.* [71–73] have presented in their meta-analysis results from 14 clinical trials presented before 1 March 2003, suggesting that CCBs were associated with a nonstatistically ($P = 0.07$) significant reduction in stroke (7.6%) vs. diuretic or β-blocker, whereas an updated overview including the 2003–2004 secondary prevention trials has demonstrated that dihydropyridine CCBs might offer a selective benefit in the prevention of stroke. Similar results were observed by Wang and coworkers [71–74] in a meta-analysis from 14 actively controlled trials compared stroke outcomes in patients randomized to various classes of antihypertensive agents. They suggest that CCBs including (−8%; $P = 0.07$) or excluding verapamil (−10%; $P = 0.02$), as well as angiotensin type 1 receptor blockers (−24%; $P = 0.0002$), resulted in

Fig. 1



Network meta-analysis of first-line treatment strategies in randomized, controlled clinical trials in hypertension. (a) Low-dose diuretics vs. placebo. (b) Low-dose diuretics vs. β-blockers. (c) Low-dose diuretics vs. angiotensin-converting enzyme (ACE) inhibitors. (d) Low-dose diuretics vs. calcium channel blockers (CCBs). (e) Low-dose diuretics vs. angiotensin receptor blockers. (f) Low-dose diuretics vs. α-blockers. Asterisks placed after the closed parentheses of the 95% CI indicate that β-blockers ($P < 0.05$), angiotensin-converting enzyme inhibitors ($P < 0.05$), CCBs ($P < 0.05$), and angiotensin-receptor blockers ($P < 0.05$) were significantly better than placebo for that outcome. Alpha-blockers were not significantly better than placebo for any outcome ($P > 0.05$). CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence interval; CVD, cardiovascular disease; RR, relative risk. Data from Psaty *et al.* [76].

better stroke prevention than the diuretics or β-blockers, whereas the opposite trend was observed for ACEI (+10%; $P = 0.03$). In a recent systematic overview by the Blood Pressure Lowering Treatment Trialists' Collaboration that estimated effects of strategies based on different antihypertensive classes of agents on the risks of major cardiovascular events and death have clearly demonstrated that compared with placebo, CCBs reduced the risk of stroke by (38%). Particularly in comparative studies, CCBs have been shown to reduce the risk of stroke more than diuretics or β-blockers [7% (−1 to 14%)], also more than ACEI therapy [12% (1–25%)]. This overview includes the data from 29 randomized trials with 162 341 patients [75].

A meta-analysis from Psaty *et al.* in 2003 summarizes the data from 42 clinical trials with 192 478 patients randomized to seven major treatment strategies, including placebo. For all outcomes, low-dose diuretics were superior to placebo: coronary heart disease, congestive heart failure, stroke, cardiovascular disease events, cardiovascular disease mortality, and total mortality. None of the first-line treatment strategies, β-blockers, ACEI, CCBs, α-blockers, and ARBs, was significantly better than low-dose diuretics for any outcome. Compared with CCBs, low-dose diuretics were associated with reduced risks of cardiovascular disease events and congestive heart failure. CCBs were superior to other treatments only for stroke prevention (Fig. 1).

Recently, a number of meta-analyses have been published that focus on the effect of CCBs compared with alternative drugs in the prevention of stroke. Angeli *et al.* [77] have published a meta-analysis of 13 studies with 103 703 patients, in which 4040 cases of stroke were reported, 1789 among 43 053 patients randomized to CCBs, and 2251 among 60 740 patients randomized to different antihypertensive drugs. They demonstrated that the risk of stroke was significantly lower among patients allocated to dihydropyridine CCBs as compared with those randomized to alternative drugs [OR: 0.90; 95% CI: 0.84–0.97; $P = 0.006$], whereas the effect of nondihydropyridine CCBs was not significant (OR: 0.92; 95% CI: 0.81–1.04). In a meta-regression analysis of these trials, the protection from stroke conferred by CCBs appeared unrelated to the degree of systolic BP reduction.

The same investigators published a meta-analysis from 28 outcome trials that compared either ACEIs or CCBs to diuretics, β-blockers, or placebo with a total of 179 122 patients and 5971 cases of stroke. In this meta-analysis, compared with diuretics/β-blockers, CCBs reduced strokes significantly ($P = 0.041$) but not ACEIs ($P = 0.15$). They [78] have confirmed that BP reduction and the use of CCBs independently reduced the incidence of stroke.

Future therapies

A soon-to-be-completed trial, Avoiding Cardiovascular Events through Combination therapy in Patients Living with Systolic Hypertension directly compared two combination therapies: benazepril and amlodipine combination with benazepril and hydrochlorothiazide combination. The study included high-risk patients with hypertension (systolic BP $\geq$ 160 mmHg or currently on antihypertensive therapy) and at least one other risk factor for cardiovascular events (prior events, target organ damage, kidney disease, or diabetes). A total of 11 454 patients were randomized with mean age (±SD) 68.4 ± 6.9 years, 60% men, and 1360 (12%) African–American. At study entry, 46% of the patients had a history of acute coronary syndromes, coronary artery bypass grafts, or percutaneous coronary interventions, and 13% had a history of stroke. A history of diabetes mellitus was reported in 6928 (60%) of patients. Mean BP at baseline (on prior hypertension therapy) was 145.4/80.0 mmHg; only 38% of patients had a BP less than 140/90 mmHg. Overall, 97% of patients had received previous antihypertensive treatment (74% were on at least two drugs); 53% were on oral diabetes therapy or insulin; 68% were on antilipid therapy; and 63% were on antiplatelet agents. The investigators hypothesize that the benazepril and amlodipine combination regimen will decrease cardiovascular events by 15% more than benazepril and hydrochlorothiazide combination. Recruitment began in 2003, and the trial is expected to conclude in 2008 [79–84].

Conclusions

CCBs are a structurally and functionally heterogeneous group of medications that are frequently used to treat patients with hypertension. As a class, they are well tolerated and exhibit a low side-effect profile. Despite concerns about their safety, recent large-scale clinical trials have found no association between long-acting CCBs and adverse cardiovascular outcomes. Even so, the use of CCBs has been associated with an increased risk of heart failure. In light of these results, it can be concluded that long-acting CCBs may be safely used in the management of hypertension and angina. As a class, however, they are not as protective as other antihypertensive agents against heart failure. All the above results indicate the use of CCBs as antihypertensive agents must be considered effective for primary or secondary stroke prevention. In comparison with other antihypertensive agents, their effects are similar to or even better than those exerted by other drugs. This may be due to the fact that stroke includes different types, with differing underlying pathophysiological mechanisms. The antiatherosclerotic properties of CCBs may be useful in preventing the atherothrombotic type of stroke at the large precerebral artery level, whereas dihydropyridinic derivatives may play a selective role in relation to small-vessel disease of the brain, which leads to multiple

stroke-associated conditions, including lacunar infarct, intra-cerebral hemorrhage and subcortical vascular dementia.

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