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Review on comparative efficacy of antihypertensive medication for prevention of cardiovascular outcomes

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Abstract
One of the main components of managing a patient with hypertension is deciding which drug to prescribe for first-line therapy. This decision should be made primarily on the basis of the best available evidence of the drug's ability to prevent adverse health outcomes of the diseases. The objective of this review is to determine the relative effects of different antihypertensive drugs in reducing the incidence of cardiovascular outcomes. Articles included in this review were randomized controlled trials and meta-analysis of RCTs. Relevant articles were obtained from Google scholar database, manual Google search and reference lists of retrieved article. Titles and abstracts were assessed for relevance and those potentially fulfilling the inclusion criteria were then assessed in full text. The following main outcomes were selected: Stroke, myocardial infarction, Coronary heart disease, heart failure, cardiovascular mortality and cardiovascular morbidity. The evidence in this review shows the newer antihypertensive drugs (CCBs and ACEIs) are better than conventional antihypertensive drugs in preventing stroke. The risk of myocardial infarction can be better reduced by using newer antihypertensive drugs like ARBs and ACEIs. All of the antihypertensive drugs did not have a significant difference in prevention of cardiovascular mortality. In hypertensive patients who had also diabetics the newer drugs have equal effectiveness with the conventional once to reduce cardiovascular mortality. The risk of myocardial infarction in this type of patients is better reduced by using ACEIs than conventional antihypertensive drugs and CCBs. CCBs are better than ACEIs to reduce the risk of stroke. ARB drugs are better for diabetic hypertensive patients to prevent cardiovascular mortality and morbidity.

Keywords: Antihypertensive medication, cardiovascular outcomes, comparative efficacy

1. Introduction
Hypertension is defined as a systolic blood pressure at or above 140 mmHg and/or a diastolic blood pressure at or above 90 mmHg. There are at least 970 million people worldwide who have elevated blood pressure (hypertension). In the developed world, about 330 million people have hypertension, as do around 640 million in the developing world. The World Health Organization rates hypertension as one of the most important causes of premature death worldwide and the problem is growing. In 2025 it is estimated there will be 1.56 billion adults living with high blood pressure [1].

Hypertension is the most important risk factor for premature cardiovascular disease, being more common than cigarette smoking, dyslipidemia, and diabetes, which are the other major risk factors. Hypertension increases the risk for a variety of cardiovascular diseases, including stroke, coronary artery disease, heart failure, and peripheral vascular disease. It accounts for an estimated 54 percent of all strokes and 47 percent of all ischemic heart disease events globally [1]. The overall goal of treating hypertension is to reduce hypertension associated morbidity and mortality. This morbidity and mortality is related to hypertension associated target-organ damage (e.g., CV events, cerebrovascular events, heart failure, and kidney disease). Reducing CV risk remains the primary purpose of hypertension therapy and the specific choice of drug therapy is significantly influenced by evidence demonstrating such CV risk reduction [2].

The last few years have seen an enormous number of randomised clinical trials and Meta analyses which have served to increase our knowledge and understanding of hypertension. One of the main components of managing a patient with hypertension is deciding which drug to prescribe for first-line therapy. This decision should be made primarily on the basis of the best available evidence of effectiveness that is the drug's ability to prevent adverse health outcomes that are important to the patient. Reliable information about the size of benefits achieved with different blood pressure lowering regimens is of great importance. If one regimen proved even slightly better than another, then preferential use of the more effective regimen might prevent tens of thousands of major cardiovascular events every year.

This review was undertaken to address the highlight of what has been done on the comparative effectiveness of different antihypertensive drugs to prevent cardiovascular outcomes. For this purpose randomized, controlled trials and Meta analytic studies of randomized trials comparing one or more drugs against each other or a placebo were selected. Since the focus was on cardiovascular event prevention ability of antihypertensive drugs, studies which compare anti-hypertensive drugs interms of fatal and non-fatal cardiovascular events like myocardial infarction, stroke, atrial fibrillation, congestive heart failure, coronary heart disease (CHD), sudden cardiac death, coronary artery disease, cardiovascular morbidity and mortality were included in the review.

2. Methods

Articles included in this review were randomized controlled trials (RCTs) and meta-analysis of RCTs. Relevant articles were obtained from Google scholar database, manual Google search and reference lists of retrieved articles. Titles and abstracts were assessed for relevance and those potentially fulfilling the inclusion criteria were then assessed in full text. The following main outcomes were selected: Stroke, myocardial infarction, Coronary heart disease, heart failure, cardiovascular mortality and cardiovascular morbidity. Non RCT studies, non English language studies, studies that have not address at least one of the main cardiovascular outcomes and abstract only articles were excluded.

3. Result

3.1 Comparison of cardiovascular outcomes between different antihypertensive drugs in non-diabetic hypertensive patients

3.1.1 Conventional anti-hypertensive drugs (diuretics and beta blockers) versus newer antihypertensive drugs (ACEIs, ARBs and CCBs)

In the study conducted to evaluate cardiovascular mortality and morbidity in elderly hypertensive patients by comparing treatment with conventional drugs (diuretics, beta-blockers) with that of newer ones [angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists], the newer therapy (ACEI/CCB) was significantly better than "conventional" therapy (diuretics/beta-blockers) in preventing all stroke in elderly patients with isolated systolic hypertension. New cases of atrial fibrillation were significantly increased by 43% (95% CI 1.02–1.99; p = 0.037) on "newer" drugs compared with "conventional" therapy, mainly attributable to the calcium antagonists. But there were no significant differences between the treatment groups with respect to the risks of myocardial infarction, sudden death or congestive heart failure. There is also no difference between the treatment groups regarding prevention of cardiovascular mortality [3].

In another study conducted in Sweden on old patients with hypertension to compare the effects of conventional and newer antihypertensive drugs on cardiovascular mortality and morbidity it is found that old and new antihypertensive drugs were similar in prevention of cardiovascular mortality or major events. According to the study the primary combined end point of fatal stroke, fatal myocardial infarction, and other fatal cardiovascular disease occurred in 221 of 2213 patients in the conventional drugs group (19.8 events per 1000 patient-years) and in 438 of 4401 in the newer drugs group (19.8 per 1000; relative risk 0.99 [95% CI 0.84-1.16], p=0.89). The combined endpoint of fatal and non-fatal stroke, fatal and non-fatal myocardial infarction, and other cardiovascular mortality occurred in 460 patients taking conventional drugs and in 887 taking newer drugs (0.96 [0.86-1.08], p=0.49) [4].

Prospectively-designed overviews with data from 29 randomised trials (n=162341) was done to estimate effects of strategies based on different drug classes (angiotensin-converting-enzyme [ACE] inhibitors, calcium antagonists, angiotensin-receptor blockers [ARBs], and diuretics or B _ blockers) or those targeting different blood pressure goals, on the risks of major cardiovascular events and death. According to this study In placebo-controlled trials the relative risks of total major cardiovascular events were reduced by regimens based on ACE inhibitors (22%; 95% CI 17–27) or calcium antagonists (18%; 5–29). Greater risk reductions were produced by regimens that targeted lower blood pressure goals (15%; 5–24). ARB-based regimens reduced the risks of total major cardiovascular events (10%; 4–17) compared with control regimens. There were no significant differences in total major cardiovascular events between regimens based on ACE inhibitors, calcium antagonists, or diuretics or B blockers, although ACE-inhibitor-based regimens reduced blood pressure less. There was evidence of some differences between active regimens in their effects on cause-specific outcomes. For every outcome other than heart failure, the difference between randomised groups in achieved blood pressure reduction was directly related to the observed difference in risk. Treatment with any commonly-used regimen reduces the risk of total major cardiovascular events, and larger reductions in blood pressure produce larger reductions in risk [5].

3.1.2 Diuretics versus other drugs

A meta analytic study done by taking 23 trials showed in the trials that had an untreated control group, low-dose thiazide therapy was associated with a significant reduction in the risk of death (RR 0.89, 95% CI 0.81–0.99), stroke (RR 0.66, 95% CI 0.56–0.79), coronary artery disease (RR 0.71, 95% CI 0.60–0.84) and cardiovascular events (RR 0.68, 95% CI 0.62–0.75). High-dose thiazide therapy, b-blocker therapy and calcium channel blocker therapy did not significantly reduce the risk of death or coronary artery disease. In both the drug–drug and the drug–no treatment comparison trials, thiazides were significantly better at reducing systolic blood pressure than the other drug classes [6].

In a randomized, double-blind, active-controlled clinical trial conducted to determine Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic, thiazide-type diuretics are superior in preventing 1 or more major forms of CVD so they should be preferred for first-step antihypertensive therapy [7].

In a prospective, randomised, double-blind trial in Europe and Israel in 6321 patients aged 55–80 years with hypertension Primary outcomes occurred in 200 (6·3%) patients in the nifedipine (CCB) group and in 182 (5·8%) in the co-amilozide (diuretic combination) group (18·2 *vs* 16·5 events per 1000 patient-years; relative risk 1·10 [95% CI 0·91–1·34], p=0·35). This shows Nifedipine once daily and co-amilozide were equally effective in preventing overall cardiovascular or cerebrovascular complications. The choice of drug can be decided by tolerability and blood-pressure response rather than long-term safety or efficacy [8].

Another study that compared the outcomes in older subjects with hypertension who were treated with angiotensin-converting– enzyme (ACE) inhibitors with the outcomes in

those treated with diuretic agents, the rates of nonfatal cardiovascular events and myocardial infarctions decreased with ACE-inhibitor treatment, whereas a similar number of strokes occurred in each group (although there were more fatal strokes in the ACE-inhibitor group). So Initiation of antihypertensive treatment involving ACE inhibitors in older subjects, particularly men, appears to lead to better outcomes than treatment with diuretic agents, despite similar reductions of blood pressure [9].

3.1.3 Conventional anti-hypertensive drugs (Diuretics and beta blockers) versus ARBs

A single blind, randomized, prospective study conducted in 1999–2002 and employing a total of 2,048 essential hypertensive subjects aged 35–79 years in Japan shows, conventional treatment was superior to candesartan (ARB)-based treatment in reducing the incidence of stroke in the patients without a past history of cardiovascular diseases (66% reduction; RR: 0.34; CI: 0.16–0.69; $p<0.05$). However ARB-based antihypertensive treatment was superior to the conventional treatment for reducing the risk of stroke and myocardial infarction, especially in the patients with a past history of cardiovascular diseases. According to this research there was a 39% reduction in hospitalization for stroke (5.8 *vs*. 9.4 cases: relative risk [RR]: 0.61; 95% confidence interval [CI]: 0.41–0.84; $p<0.05$) and a 57% reduction in hospitalization for myocardial infarction (RR: 0.44; CI: 0.21–0.84; $p<0.05$) with the candesartan-based treatment compared with the conventional treatment. In spite of this there was no significant reduction in the incidence of congestive heart failure (15% reduction: 4.3*vs*. 5.0; RR: 0.85; CI: 0.57–1.26) [10].

3.1.4 Conventional anti-hypertensive drugs (Diuretics and beta blockers) versus ACEIs or CCBs

A meta-analysis study done by extracting summary statistics regarding CHD and stroke from 28 outcome trials that compared either ACEIs or CCBs with diuretics, β-blockers, or placebo for a total of 179 122 patients, shows there were no significant differences in CHD risk between regimens based on diuretics/β-blockers and regimens based on ACEIs (P=0.46) or CCBs (P=0.52). The risk of stroke was reduced by CCBs (P=0.041) but not by ACEIs (P=0.15) compared with diuretics/β-blockers. Prevention of CHD was explained by systolic BP reduction (P<0.001) and use of ACEIs (P=0.028), whereas prevention of stroke was explained by systolic BP reduction (P=0.001) and use of CCBs (P=0.042). These findings confirm that BP lowering is fundamental for prevention of CHD and stroke. However, over and beyond BP reduction, ACEIs appear superior to CCBs for prevention of CHD, whereas CCBs appear superior to ACEIs for prevention of stroke [11].

A randomised intervention trial conducted in Sweden and Finland to compare the effects of ACE inhibition and conventional therapy on cardiovascular morbidity and mortality in patients with hypertension ACE inhibitor (Captopril) and conventional treatment did not differ in efficacy in preventing cardiovascular morbidity and mortality [12].

3.1.5 Comparative effectiveness of the newer antihypertensive drugs (ARBs, CCBs, ACEIs)

A study designed to compare the long-term effects of the angiotensin II receptor blocker (candesartan) and the calcium channel blocker (amlodipine) on the incidence of cardiovascular events, represented as a composite of sudden death and cerebrovascular, cardiac, renal, and vascular events in high-risk Japanese hypertensive patients shows the 2 treatment-based regimens produced no significant differences in cardiovascular morbidity or mortality in the high-risk Japanese hypertensive patients (hazard ratio: 1.01; 95% CI: 0.79 to 1.28; P_0.969). In each primary end point category, there was no significant difference between the 2 treatment-based regimens. New-onset diabetes occurred in fewer patients taking candesartan (8.7/1000 person-years) than in those taking amlodipine (13.6/1000 person-years), which resulted in a 36% relative risk reduction (hazard ratio: 0.64; 95% CI: 0.43 to 0.97; P_0.033) [13].

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial was designed to test the hypothesis that for the same blood-pressure control, valsartan would reduce cardiac morbidity and mortality more than amlodipine in hypertensive patients at high cardiovascular risk. According to this study Blood pressure was reduced by both treatments, but the effects of the amlodipine-based regimen were more pronounced, especially in the early period (blood pressure 4·0/2·1 mm Hg lower in amlodipine than valsartan group after 1 month; 1·5/1·3 mm Hg after 1 year; p<0·001 between groups). The primary composite endpoint 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). Therefore the main outcome of cardiac disease did not differ between the treatment groups [14].

A meta-analysis performed by taking 20 cardiovascular morbidity–mortality trials to analyse the effects of RAAS inhibitors as a class of drugs, as well as of angiotensin-converting enzyme (ACE) inhibitors and AT1 receptor blockers (ARBs) separately, on all-cause mortality shows RAAS inhibition was associated with a 5% reduction in all-cause mortality (HR: 0.95, 95% CI: 0.91–1.00, P ¼ 0.032), and a 7% reduction in cardiovascular mortality (HR: 0.93, 95% CI: 0.88–0.99, P ¼ 0.018). The observed treatment effect resulted entirely from the class of ACE inhibitors, which were associated with a significant 10% reduction in all-cause mortality (HR: 0.90, 95% CI: 0.84–0.97, P ¼ 0.004), whereas no mortality reduction could be demonstrated with ARB treatment (HR: 0.99, 95% CI: 0.94–1.04, P ¼ 0.683). This difference in treatment effect between ACE inhibitors and ARBs on all-cause mortality was statistically significant (P-value for heterogeneity 0.036) (15).

The overview of placebo-controlled trials of ACE inhibitors (4 trials, 12124 patients mostly with coronary heart disease) revealed reductions in stroke (30% [95% CI 15–43]), coronary heart disease (20% [11–28]), and major cardiovascular events (21% [14–27]). The overview of placebo-controlled trials of calcium antagonists (two trials, 5520 patients mostly with hypertension) showed reductions in stroke (39% [15–56]) and major cardiovascular events (28% [13–41]). In the overview of trials comparing blood pressure- lowering strategies of different intensity (three trials, 20408 patients with hypertension), there were reduced risks of stroke (20% [2–35]), coronary heart disease (19% [2–33]), and major cardiovascular events (15% [4–24]) with more intensive therapy. In the overviews comparing different antihypertensive regimens (eight trials, 37872 patients with hypertension), several differences in cause-specific effects were seen between calcium antagonist- based therapy and other regimens, but

each was of borderline significance. Strong evidence of benefits of ACE inhibitors and calcium antagonists is provided by the overviews of placebo-controlled trials. There is weaker evidence of differences between treatment regimens of differing intensities and of differences between treatment regimens based on different drug classes [16].

3.2 Comparisons of cardiovascular outcomes between different antihypertensive drugs in hypertensive patients who have diabetics

The benefits of treating hypertension in elderly diabetic patients, in terms of achieving reductions in cardiovascular morbidity and mortality, have been documented in several recent prospective trials. There has, however, been some controversy regarding the effect of different antihypertensive drugs on the frequency of cardiovascular events in this group of patients.

3.2.1 Conventional anti-hypertensive drugs (Diuretics and beta blockers) versus newer antihypertensive drugs (ACEIs, ARBs and CCBs)

In one of a prospective, randomized, open trial with blinded endpoint evaluation treatment of hypertensive diabetic patients with conventional antihypertensive drugs (diuretics, β-blockers, or both) seemed to be as effective as treatment with newer drugs such as calcium antagonists or ACE inhibitors. In this study 6614 elderly patients aged 70-84 years; 719 of them had diabetes mellitus at the start of the study (mean age 75.8 years) were randomly assigned to one of three treatment strategies: conventional antihypertensive drugs (diuretics or β-blockers), calcium antagonists, or angiotensin converting enzyme (ACE) inhibitors. Reduction in blood pressure was similar in the three treatment groups of diabetics. The prevention of cardiovascular mortality was also similar; the frequency of this primary endpoint did not differ significantly between the three groups. There were, however, significantly fewer ($P = 0.025$) myocardial infarctions during ACE inhibitor treatment ($n = 17$) than during calcium antagonist treatment ($n = 32$; relative risk 0.51, 95% confidence interval 0.28-0.92); but a (non-significant) tendency to more strokes during ACE inhibitor treatment ($n = 34$ compared with $n = 29$; relative risk 1.16, 95% confidence interval 0.71-1.91) [17].

In another study done in diabetic patients to compare the effects of losartan and atenolol on cardiovascular morbidity and mortality, Losartan was found to be more effective than atenolol in reducing cardiovascular morbidity and mortality as well as mortality from all causes. This shows Losartan seems to have benefits beyond blood pressure reduction than atenolol [18].

The Captopril Prevention Project (CAPPP) evaluated the effects of an ACE inhibitor–based therapeutic regimen on cardiovascular mortality and morbidity in hypertension. The study takes 572 hypertensive patients who had diabetes at baseline and were studied according to a prospective, randomized, open, blinded end point trial design. The patients were randomized to receive either captopril or conventional antihypertensive treatment (diuretics and/or β-blockers). The primary end point, fatal and nonfatal myocardial infarction and stroke as well as other cardiovascular deaths, was markedly lower in the captopril than in the conventional therapy group (relative risk [RR] = 0.59; $P = 0.018$). Specifically, cardiovascular mortality, defined as fatal stroke and myocardial infarction, sudden death, and other cardiovascular death, tended to be lower in the captopril group (RR = 0.48; $P = 0.084$), and no difference was observed between the study groups for stroke (RR = 1.02; $P = 0.96$). Myocardial infarctions were less frequent in the captopril group than in the conventional therapy group (RR = 0.34; $P = 0.002$). Furthermore, total mortality was lower in the captopril as compared with the conventional therapy group (RR = 0.54; $P = 0.034$). Patients with impaired metabolic control seemed to benefit the most from ACE inhibitor–based therapy [19].

3.2.2 Comparative effectiveness of the newer antihypertensive drugs (ARBs, CCBs, ACEIs)

Study of Comparison Between Valsartan and Amlodipine Regarding Cardiovascular Morbidity and Mortality in Hypertensive Patients With Glucose Intolerance shows Patients in the valsartan group had a significantly lower incidence of heart failure than in the amlodipine group (hazard ratio: 0.20 [95% CI: 0.06–0.69]; P_0.01). Other components and all-cause mortality were not significantly different between the 2 groups. Composite cardiovascular outcomes were comparable between the valsartan- and amlodipine based treatments in Japanese hypertensive patients with glucose intolerance. Admission because of heart failure was significantly less in the valsartan group [20].

Study on the incidence of cardiovascular complications in patients with non-insulin-dependent diabetes mellitus and hypertension who were randomly assigned to treatment with either the calcium-channel blocker (nisoldipine) or the angiotensin-converting– enzyme inhibitor (enalapril) shows nisoldipine was associated with a higher incidence of fatal and nonfatal myocardial infarctions (a total of 25) than enalapril (total, 5) (risk ratio 9.5; 95 percent confidence interval, 2.3 to 21.4) [21].

Table 1: Comparison of the effect of antihypertensive drugs on cardiovascular outcomes

	Cardiovascular outcome	comparision	reference
Comparison of Antihypertensive drugs in non-diabetic patients	Preventing Stroke	New > conventional	3*
		conventional > ARB (candesartan)	8#
		ARB (candesartan) >conventional	8”
		CCB > conventional	9
		ACEI < CCB	16
	atrial fibrillation incidence	New(CCB)> conventional	3*
	Reduction in the risk of myocardial infarction	New =conventional	3*
		ARB (candesartan) >conventional	8”
		ACEI > diuretics	10
		Diuretics >BB	16
	Prevention of heart failure	New =conventional	3*
		ACEI > CCB	16
		Diuretics > CCB/BB/α Blocker	16
	prevention of cardiovascular mortality	New =conventional	3*
		New =conventional	4
		ACE(captopril)=conventional	5
		ACEI (Candesartan) =CCB (amlodipine)	12
		Valsartan(ARB) = amlodipine(CCB)	13
	prevention of cardiovascular morbidity	ACE(captopril)=conventional	5
		Diuretics(tiazide)>ACEI/CCB	7
		ACEI > diuretics	10 ¤
		ACEI (Candesartan) =CCB (amlodipine)	12
		Valsartan(ARB) = amlodipine(CCB)	13
	Reduction of CHD risk	New (ACEI/CCB) =conventional	9
Comparison of Antihypertensive drugs in diabetic patients	Reduction in the risk of myocardial infarctions	ACEI > CCB	17
		ACEI (captopril) > conventional	19
		ACEI (enalapril) >CCB(nisoldipine)	21
	Reduction in the risk Stroke	ACEI < CCB	17
		ACEI (captopril) = conventional	19
	prevention of cardiovascular mortality	Losartan (ARB) > atenolol (BB)	18
		New (ACEI/CCB) =conventional	17
	prevention of cardiovascular morbidity	Losartan (ARB) > atenolol (BB)	18
	Prevention of heart failure	Valsartan (ARB) >amlodipine(CCB)	20^

*- For elderly patients with isolated systolic hypertension
-essential hypertensive patients without a past history of cardiovascular diseases
“-essential hypertensive patients with a past history of cardiovascular diseases
^ -hypertensive patients with glucose intolerance.
Π -Male hypertensive patients

Table 2: Summary of descriptive review of articles

Topic	Purpose	Design & sample	Outcomes and Intervention	Results	Conclusions & Implications
Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic: 2002	To determine whether treatment with a calcium channel blocker or an angiotensin converting enzyme inhibitor lowers the incidence of coronary heart disease (CHD) or other cardiovascular disease (CVD) events vs treatment with a diuretic	-A randomized, double-blind, active-controlled clinical trial. -A total of 33,357 participants aged 55 years or older with hypertension and at least 1 other CHD risk factor from 623 North American centers	-chlorthalidone, 12.5 to 25 mg/d (n = 15 255); amlodipine, 2.5 to 10 mg/d (n = 9048); or lisinopril, 10 to 40 mg/d (n = 9054) for planned follow-up of approximately 4 to 8 years. -The primary outcome was combined fatal CHD or nonfatal myocardial infarction, analyzed by intent-to-treat. -Secondary outcomes were mortality, stroke, combined CHD and combined CVD	-Compared with chlorthalidone, the relative risks were 0.98 for amlodipine and 0.99 for lisinopril -mortality did not differ between groups -For amlodipine vs chlorthalidone, secondary outcomes were similar except for a higher 6-year rate of HF with amlodipine (10.2% vs 7.7%; RR, 1.38. -lisinopril had higher 6-year rates of combined CVD (33.3% vs 30.9%; RR, 1.10; stroke (6.3% vs 5.6%; RR, 1.15; and HF (8.7% vs 7.7%; RR, 1.19;	Thiazide-type diuretics are superior in preventing 1 or more major forms of CVD
Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic 2000	To compare the effects of the calcium-channel blocker, nifedipine once daily with the diuretic combination coamilozide on cardiovascular mortality and morbidity in high risk patients with hypertension.	a prospective, randomised, double-blind trial in Europe and Israel in 6321 patients aged 55–80 years with hypertension Patients are at risk to develop cardiovascular disease	nifedipine 30 mg in a long-acting formulation (n=3157), or co-amilozide (hydrochlorothiazide 25g plus amiloride 2·5 mg; n=3164). -The primary outcome was cardiovascular death, myocardial infarction, heart failure, or stroke.	Primary outcomes occurred in 200 (6·3%) patients in the nifedipine group and in 182 (5·8%) in the co-amilozide group (18·2 *vs* 16·5 events per 1000 patient-years; relative risk 1·10 [95% CI 0·91–1·34], p=0·35).	Nifedipine once daily and co-amilozide were equally effective in preventing overall cardiovascular or cerebrovascular complications.
Effects of Candesartan Compared With Amlodipine in Hypertensive Patients With High Cardiovascular Risks 2008	to compare the long-term effects of the angiotensin II receptor blocker, candesartan and the calcium channel blocker, amlodipine on the incidence of cardiovascular events, in high-risk Japanese hypertensive patients.	prospective, randomized, open-label study with blinded assessment of the end point in 4728 Japanese hypertensive patients (mean age: 63.8 years; mean body mass index: 24.6 kg/m2). Patients were followed for an average of 3.2 years.	-Primary end points (composite of the following events) Sudden death: unexpected death that happened within 24 hours without external causes Cerebrovascular events: stroke or transient ischemic attack Cardiac events: heart failure, angina pectoris, or acute myocardial infarction Renal events: serum creatinine concentration _4.0 mg/dL, doubling of the serum creatinine concentration (however, creatinine _2.0 mg/dL is not regarded as an event), or end-stage renal disease Vascular events: dissecting aortic aneurysm or arteriosclerotic occlusion of a peripheral artery -Secondary and prespecified end points All-cause deaths, New-onset diabetes Discontinuance of treatment because of adverse events **Intervention** Candesartan cilexetil (4 to 8 mg/d. When the patient's blood pressure (BP) did not reach the targets for controlled BP, the dose was increased to 12 mg/d.) or amlodipine besylate (2.5 to 5.0 mg/d and was increased to 10.0 mg/d when necessary).	Primary cardiovascular events occurred in 134 patients with both the candesartan- and amlodipine-based regimens. The 2 treatment-based regimens produced no significant differences in cardiovascular morbidity or mortality in the high-risk Japanese hypertensive patients (hazard ratio: 1.01; 95% CI: 0.79 to 1.28; *P*_0.969). In each primary end point category, there was no significant difference between the 2 treatment-based regimens. New-onset diabetes occurred in fewer patients taking candesartan (8.7/1000 person-years) than in those taking amlodipine (13.6/1000 person-years), which resulted in a 36% relative risk reduction (hazard ratio: 0.64; 95% CI: 0.43 to 0.97; *P*_0.033).	candesartan-based and amlodipinebased regimens produced no statistical differences in terms of the primary cardiovascular end point, whereas candesartan prevented new-onset diabetes more effectively than amlodipine.

A Comparison of Outcomes with Angiotensin-Converting–Enzyme Inhibitors and Diuretics for Hypertension in the Elderly 2003	To test the hypothesis that agents which inhibit the renin–angiotensin system confer benefit beyond the reduction of blood pressure alone.	a prospective, randomized, open-label study with blinded assessment of end points in 6083 subjects (95 percent of whom were white) with hypertension who were 65 to 84 years of age and received health care at 1594 family practices. Subjects were followed for a median of 4.1 years	coronary events, including myocardial infarction, sudden or rapid death from cardiac causes, other deaths from coronary causes, or coronary events associated with therapeutic procedures involving the coronary arteries; other cardiovascular events, including heart failure, acute occlusion of a major feeding artery in any vascular bed other than cerebral or coronary, death from noncoronary cardiac causes, dissecting or ruptured aortic aneurysm, or death from vascular causes; and cerebrovascular events, including stroke and transient ischemic attacks. 3044 subjects were assigned to the ACE-inhibitor 3039 subjects were assigned to the diuretic group. Subjects were recruited over a 3-year period and were followed for a median of 4.1 years, for a total of 24,702 patient-years of observation.	There were 695 cardiovascular events or deaths from any cause in the ACE-inhibitor group (56.1 per 1000 patient-years) and 736 cardiovascular events or deaths from any cause in the diuretic group (59.8 per 1000 patient years; the hazard ratio for a cardiovascular event or death with ACE-inhibitor treatment was 0.89 [95 percent confidence interval, 0.79 to 1.00]; P=0.05). The rates of nonfatal cardiovascular events and myocardial infarctions decreased with ACE-inhibitor treatment, whereas a similar number of strokes occurred in each group (although there were more fatal strokes in the ACE-inhibitor group).	Initiation of antihypertensive treatment involving ACE inhibitors in older subjects, particularly men, appears to lead to better outcomes than treatment with diuretic agents, despite similar reductions of blood pressure
Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension. (1999)	to compare the effects of ACE inhibition and conventional therapy on cardiovascular morbidity and mortality in patients with hypertension.	-prospective, randomised, open trial with blinded endpoint evaluation. 10985 patients were enrolled at 536 health centres in Sweden and Finland. -Patients aged 25–66 years with a measured diastolic blood pressure of 100 mm Hg or more	The primary endpoint was a composite of fatal and non-fatal myocardial infarction, stroke, and other cardiovascular deaths. **intervention** captopril or conventional antihypertensive treatment (diuretics, b-blockers, or both). The initial dose of captopril was 50 mg daily given in one or two doses. In the group receiving conventional treatment, atenolol and metoprolol were the most commonly used b-blockers, and hydrochlorothiazide and bendrofluazide the most common diuretics. The initial dose of atenolol and metoprolol was 50–100 mg once daily. Hydrochlorothiazide was given as 25 mg once daily, and bendrofluazide as 2·5 mg once daily.	-Primary endpoint events occurred in 363 patients in the captopril group (11·1 per 1000 patient years) and 335 in the conventional-treatment group (1 0 · 2 per 1000 patient-years; relative risk 1·05 [95% CI 0·90–1·22], p=0·52). -Cardiovascular mortality was lower with captopril than with conventional treatment (76 *v s* 9 5 events; relative risk 0·77 [0·57–1·04], p=0·092), the rate of fatal and non-fatal myocardial infarction was similar (162 *v s* 161), but fatal and non-fatal stroke was more common with captopril (189 vs 148; 1·25 [1·01–1·55]. p=0·044).	-Captopril and conventional treatment did not differ in efficacy in preventing cardiovascular morbidity and mortality. -The difference in stroke risk is probably due to the lower levels of blood pressure obtained initially in previously treated patients randomised to conventional therapy.

Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: 2004	to test the hypothesis that for the same blood-pressure control, valsartan would reduce cardiac morbidity and mortality more than amlodipine in hypertensive patients at high cardiovascular risk.	-randomised, double-blind, parallel-group comparison study -15 245 patients, aged 50 years or older with treated or untreated hypertension and high risk of cardiac events participated in therapy based on valsartan or amlodipine. -Duration of treatment was event-driven and the trial lasted until at least 1450 patients had reached a primary endpoint, Patients from 31 countries were followed up for a mean of 4—2 years.	cardiac mortality and morbidity **intervention** valsartan and amlodipine	The primary composite endpoint 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).	The main outcome of cardiac disease did not differ between the treatment groups.
Effects of candesartan on cardiovascular outcomes in Japanese hypertensive patients. 2005	To determine whether ARBs are effective for protecting against hypertensionrelated organ damage in the general Japanese population	single blind, randomized, prospective study conducted in 1999-2002 and employing a total of 2,048 essential hypertensive subjects (sitting blood pressure 140-180/90 110 mmHg) aged 35-79 years.	Subjects were randomly assigned to receive the ARB candesartan, 2 to 12 mg daily, or conventional antihypertensive drugs other than angiotensin converting enzyme inhibitors or ARBs. The primary outcome was assessed by hospitalization due to stroke, myocardial infarction, and congestive heart failure.	There was a 39% reduction in hospitalization for stroke (5.8 vs. 9.4 cases: relative risk [RR]: 0.61; 95% confidence interval [CI]: 0.41-0.84; $p<0.05$) and a 57% reduction in hospitalization for myocardial infarction (RR: 0.44; CI: 0.21-0.84; $p<0.05$) with the candesartan-based treatment compared with the conventional treatment. In spite of a significant difference in the total incidence of both stroke and myocardal infarction, there was no significant reduction in the incidence of congestive heart failure (15% reduction: 4.3 vs. 5.0; RR: 0.85; CI: 0.57-1.26). -Further analysis in stratifying the subjects with or without a past history of cardiovascular diseases including stroke and myocardal infarction revealed that candesartan reduced the incidence of stroke (61% reduction; RR: 0.39; CI: 0.15-0.43; $p<0.01$) and congestive heart failure (49% reduction; RR: 0.51; CI: 0.23-0.92; $p<0.05$) but not myocardial infarction (RR: 0.74; CI: 0.36-1.48; $p=0.1$) in hypertensive patients with a past history. However, conventional treatment was superior to candesartan-based treatment in reducing the incidence of stroke in the patients without a past history of cardiovascular diseases (66% reduction; RR: 0.34; CI: 0.16-0.69; $p<0.05$).	ARB-based antihypertensive treatment was superior to the conventional treatment for reducing the risk of stroke and myocardial infarction in Japanese hypertensive patients, especially in the patients with a past history of cardiovascular diseases.

Cardiovascular events in elderly patients with isolated systolic hypertension.	To evaluate cardiovascular mortality and morbidity in elderly hypertensives comparing treatment with conventional drugs (diuretics, beta-blockers) with that of newer ones (ACEinhibitors, calcium antagonists].	Randomized trial 6614 elderly patients with hypertension (mean age 76.0 years, range 70-84 years at baseline) were included. Among these 2280 patients had isolated systolic hypertention	patients were randomized to one of three treatment groups: "conventional" antihypertensive therapy with beta-blockers or diuretics (atenolol 50 mg, metoprolol 100 mg, pindolol 5 mg, or fixed-ratio hydrochlorothiazide 25 mg plus amiloride 2.5 mg daily); ACE inhibitors (enalapril 10 mg or lisinopril 10 mg daily); or calcium antagonists (felodipine 2.5 mg or isradipine 2.5 mg daily). -Analysis was by intention to treat. the primary endpoints of the study were cardiovascular mortality, fatal and non-fatal stroke	All stroke events, i.e. fatal and non-fatal stroke together, were significantly reduced by 25% in the newer-drugs group compared with the conventional group (95% CI 0.58-0.97; p=0.027). This difference was attributable to reduction of non-fatal stroke while fatal stroke events did not differ between groups. New cases of atrial fibrillation were significantly increased by 43% (95% CI 1.02-1.99; p=0.037) on "newer" drugs compared with "conventional" therapy, mainly attributable to the calcium antagonists. There were no significant differences between the three treatment groups with respect to the risks of myocardial infarction, sudden death or congestive heart failure.	(ACE inhibitors/calcium antagonists) was significantly better (25%) than "conventional" (diuretics/beta-blockers) in preventing all stroke in elderly patients with isolated systolic hypertension.
Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension 1999	To compare the effects of conventional (diuretics and beta blokers) and newer antihypertensive (ACEI)drugs on cardiovascular mortality and morbidity in elderly patients.	prospective, randomised trial in 6614 patients aged 70-84 years with hypertension (blood pressure > or = 180 mm Hg systolic, > or = 105 mm Hg diastolic, or both).	Patients were randomly assigned to conventional antihypertensive drugs (atenolol 50 mg, metoprolol 100 mg, pindolol 5 mg, or hydrochlorothiazide 25 mg plus amiloride 2.5 mg daily) or newer drugs (enalapril 10 mg or lisinopril 10 mg, or felodipine 2.5 mg or isradipine 2-5 mg daily). -Out comes were fatal stroke, fatal myocardial infarction, and other fatal cardiovascular disease. -Analysis was by intention to treat.	The primary combined endpoint of fatal stroke, fatal myocardial infarction, and other fatal cardiovascular disease occurred in 221 of 2213 patients in the conventional drugs group (19.8 events per 1000 patient-years) and in 438 of 4401 in the newer drugs group (19.8 per 1000; relative risk 0.99 [95% CI 0.84-1.16], p=0.89). The combined endpoint of fatal and non-fatal stroke, fatal and non-fatal myocardial infarction, and other cardiovascular mortality occurred in 460 patients taking conventional drugs and in 887 taking newer drugs (0.96 [0.86-1.08], p=0.49).	Old and new antihypertensive drugs were similar in prevention of cardiovascular mortality or major events. Decrease in blood pressure was of major importance for the prevention of cardiovascular events.
Comparison Between Valsartan and Amlodipine Regarding Cardiovascular Morbidity and Mortality in Hypertensive Patients With Glucose Intolerance	To compare the efficacies on cardiovascular outcomes between ARB and CCB in hypertensive patients with glucose intolerance.	- prospective, open-labeled, randomized, controlled trial -A total of 1150 patients (women: 34%; mean age: 63 years; diabetes mellitus: 82%) The median follow-up period was 3.2 years.	Primary outcome was a composite of acute myocardial infarction, stroke, coronary revascularization, admission attributed to heart failure, or sudden cardiac death.	primary outcome had occurred in 54 patients in the valsartan group and 56 in the amlodipine group (hazard ratio: 0.97 [95% CI: 0.66 –1.40]; *P*_0.85). Patients in the valsartan group had a significantly lower incidence of heart failure than in the amlodipine group (hazard ratio: 0.20 [95% CI: 0.06–0.69]; *P*_0.01). Other components and all-cause mortality were not significantly different between the 2 groups.	Composite cardiovascular outcomes were comparable between the valsartan- and amlodipinebased Treatment -Admission because of heart failure was significantly less in the valsartan group
Comparison of antihypertensive treatments in preventing cardiovascular events in elderly diabetic patients: results from the Swedish Trial in Old Patients with Hypertension-2. STOP Hypertension-2 Study Group. 2000	To determine the effect of different antihypertensive drugs on the frequency of myocardial infarction in elderly diabetic patients	prospective, randomized, open trial with blinded endpoint evaluation 6614 elderly patients aged 70-84 years; 719 of them had diabetes mellitus at the start of the study (mean age 75.8 years).	Patients were randomly assigned to one of the three treatment strategies: conventional antihypertensive drugs (diuretics or beta-blockers), calcium antagonists, or angiotensin converting enzyme (ACE) inhibitors. primary endpoints were.	Reduction in blood pressure was similar in the three treatment groups of diabetics. The prevention of cardiovascular mortality was also similar; the frequency of this primary endpoint did not differ significantly between the three groups. There were, however, significantly fewer (P = 0.025) myocardial infarctions during ACE inhibitor treatment (n = 17) than during calcium antagonist treatment (n = 32; relative risk 0.51, 95% confidence interval 0.28-0.92); but a (non-significant) tendency to more strokes during ACE inhibitor treatment (n = 34 compared with n = 29; relative risk 1.16, 95% confidence interval 0.71-1.91).	Treatment of hypertensive diabetic patients with conventional antihypertensive drugs (diuretics, beta-blockers, or both) seemed to be as effective as treatment with newer drugs such as calcium antagonists or ACE inhibitors

4. Conclusion

As compared to placebo every antihypertensive drug reduces the risk of total major cardiovascular events. CCBs and ACEIs are better than diuretics and beta blockers in preventing stroke. CCB are far more superior in reducing the risk of stroke than ACEIs. For essential hypertensive patients the ability of the drug to prevent stroke depends on the previous cardiovascular disease history.

The risk of myocardial infraction can be better reduced by using ARBs and ACEIs. But these two drug classes are found to be equally effective in patients with isolated systolic hypertension. Diuretics should be preferred than beta blockers in order to reduce the risk of myocardial infraction. ACEIs and diuretics are superior to CCB, beta blockers and alfa blockers in preventing heart failure in hypertensive patients. All of the antihypertensive drugs did not have a significant difference in prevention of cardiovascular mortality. ACEI, CCB and ARB drugs are equally effective in their ability to reduce cardiovascular morbidity. Thiazide-type diuretics are superior than CCB and ACEI in preventing cardiovascular morbidity.

In hypertensive patients who had also diabetics ACEI and CCB have equal effectiveness with diuretics and beta blockers to reduce cardiovascular mortality. The risk of myocardial infraction in this type of patients is better reduced by using ACEIs than diuretics, beta blockers and CCBs. CCB are better than ACEIs to reduce the risk of stroke. Losartan is better for diabetic hypertensive patients to prevent cardiovascular mortality and morbidity than atenolol. Valsartan is better than amlodipine to prevent heart failure risk in this type of patients.

5. Abbreviations

ACEI Angiotensin Converting Enzyme Inhibitor
ARB Angiostension Receptor Blocker
BB Beta Blocker
CCB Calcium Channel Blocker
CHD Coronary Heart Disease
CV Cardio-Vascular
RCT Randomized Controlled Trial
SBP Systolic Blood Pressure

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