

EVIDENCE-BASED CLINICAL MEDICINE

Are Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers Especially Useful for Cardiovascular Protection?

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Purpose: This article seeks to objectively review the clinical trial evidence to determine whether angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) have special cardiovascular protective effects.

Methods: An objective review of the clinical trial evidence.

Results: Clinical trials in hypertensive patients comparing ACEI and ARB with other drugs generally showed no difference in the primary cardiovascular outcome (United Kingdom Prospective Diabetes Study Group, Captopril Prevention Project, Swedish Trial in Old Patients with Hypertension 2, Japan Multicenter Investigation for Cardiovascular Diseases-B Randomized Trial, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, Second Australian National Blood Pressure Study Group, Valsartan Antihypertensive Long-Term Use Evaluation). Where the primary, or major secondary, cardiovascular end-point favors one of the treatment arms, it was always the arm with the lower achieved blood pressure that saw the better clinical result as in Losartan Intervention For Endpoint Reduction in Hypertension Study, Captopril Prevention Project, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, and Valsartan Antihypertensive Long-Term Use Evaluation. Trials comparing ACEI or ARB against placebo in patients at high risk of cardiovascular events have not showed a consistent result; cardiovascular outcomes were reduced in Heart Outcomes Prevention Evaluation, European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease, and the Jikei Heart Study, but were not significantly reduced in Perindopril Protection Against Recurrent Stroke Study, Comparison of Arnlodipine vs Enalapril to Limit Occurrences of Thrombosis Trial, Prevention of Events with ACEIs Trial, Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects with Cardiovascular Disease Trial, and Prevention Regimen for Effectively Avoiding Second Strokes Trial. In the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial, combining ACEIs with ARBs in high-risk patients did not reduce cardiovascular or renal outcomes compared with ACEI monotherapy alone. This absence of a reduction in cardiovascular outcome from the ACEI and ARB combination arm is further evidence suggesting that these drugs do not have any special cardiovascular protective effect. This objective review thus shows that the rennin-angiotensin antagonists do not have special cardiovascular protective properties.

Conclusion: The key to reducing cardiovascular outcome is to appropriately control blood pressure as well as to treat all other coronary risk factors. (J Am Board Fam Med 2009;22:686–697.)

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) produce

no metabolic adverse consequences and are said to have special cardiovascular protective effects in high-risk patients.^{1–4} However, recent clinical trials have shown that practical reality may be different from theoretical benefit, and improvement of metabolic parameters did not produce the expected reduction of clinical outcomes in diabetes and dyslipidemia.^{5,6} This article seeks to objectively review the trial evidence to determine whether ACEIs and ARBs do indeed have special cardiovascular protective properties.

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Method

A PubMed search was conducted using the keywords “hypertension,” “high risk,” “coronary disease,” “cardiovascular outcome,” “ACEIs,” “ARBs,” and “randomized, controlled, trials.” The results were supplemented by references of the retrieved articles, as well as the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; the World Health Organization; the British Hypertension Society/National Institute for Health and Clinical Excellence; and the European hypertension guidelines. Trials selected were prospective, randomized (level 1 study quality) trials recruiting more than 500 patients, had follow-up of more than 2 years, and had clinical primary endpoints. Two types of trials were indentified: those in hypertensive patients where ACEIs/ARBs were compared with other antihypertensive drugs and those in which ACEIs/ARBs were compared with placebo among patients at high cardiovascular risk.

Do ACEIs Have Special Cardiovascular Protective Effects?

Trials assessing the value of ACEIs in reducing cardiovascular disease can be divided into 2 types: (1) those comparing ACEIs with other drugs in hypertensive patients, and (2) those comparing ACEIs with placebo among patients at high cardiovascular risk who actually have a combination of diabetes, hypertension, hyperlipidemia, and pre-existing clinical atherosclerotic disease.

Clinical trials comparing ACEIs with other antihypertensive drugs generally showed no difference in cardiovascular outcome (Table 1). In the United Kingdom Prospective Diabetes Study Group, 758 hypertensive diabetics had their blood pressure (BP) tightly controlled with either captopril or atenolol.⁷ Both treatment arms had similar BP reduction and after 9 years there was no difference in the primary outcome of diabetic-related clinical events (relative risk [RR] for captopril, 1.10; 95% CI, 0.86–1.41); stroke (RR, 1.12; 95% CI, 0.59–2.12); myocardial infarction (MI) (RR, 1.20; 95% CI, 0.82–1.76), or total mortality (RR, 1.14; 95% CI, 0.81–1.61). In contrast, cardiovascular events were much higher among patients who maintained less strict BP levels compared with the group on tight BP control.¹⁵

CAPPP randomized 10,985 hypertensive patients to either captopril or conventional diuretics or β -blockers.⁸ BP reduction was equal with both regimes, although the captopril group had a higher BP at randomization and throughout the study. After 6.1 years, the composite primary endpoint of MI, stroke, or cardiovascular death was not significantly different (RR with captopril 1.05; 95% CI, 0.90–1.22). Although MI, cardiovascular mortality, total mortality, and cardiac events were all similar, patients using captopril had higher stroke (RR, 1.25; 95% CI, 1.01–1.55) and lower diabetes (RR, 0.86; 95% CI, 0.74–0.99). The Swedish Trial in Old Patients with Hypertension 2 recruited 6614 older hypertensive patients and randomized them to conventional therapy (β -blockers or diuretics), calcium channel-blockers (CCBs), or ACEIs.⁹ Reduction in BP was similar in the 3 groups. After 4 to 6 years there was no difference in cardiovascular mortality—the primary endpoint—between conventional therapy (19.8 per 1000 patient-years), ACEIs (20.5 per 1000 patient-years), or CCBs (19.2 per 1000 patient-years). Cardiovascular mortality, MI, stroke, total mortality, diabetes, and heart failure were also equal in these 3 groups.

ALLHAT was the largest clinical hypertensive study ever conducted comparing doxazosin ($n = 9061$), amlodipine ($n = 9048$), and lisinopril ($n = 9054$) with the diuretic chlorthalidone ($n = 15,255$).^{11,16} The doxazosin arm was terminated early after a median of 3.2 years; systolic BP was approximately 2 mm Hg higher with doxazosin.¹⁶ Although the primary outcome of fatal coronary heart disease and nonfatal MI was equal among patients taking either treatment, the doxazosin arm had more stroke (RR, 1.26; 95% CI, 1.10–1.46), heart failure (RR, 1.80; 95% CI, 1.61–2.02), and combined cardiovascular events (RR, 1.20; 95% CI, 1.13–1.27). The remaining patients had a longer mean follow-up of 4.9 years.¹¹ Systolic BP was higher in patients taking amlodipine (0.8 mm Hg; $P = .03$) and lisinopril (2 mm Hg; $P < .001$) than in those using chlorthalidone. The 6-year primary endpoint rate was not significantly different on the diuretic chlorthalidone (11.5%); CCBs (11.3%; RR, 0.98; 95% CI, 0.90–1.07), or ACEIs (11.4%; RR, 0.99; 95% CI, 0.91–1.08). However, compared with the diuretic, the CCB arm had higher heart failure (RR, 1.38, 95% CI, 1.25–1.52) whereas the ACEI arm had higher heart failure (RR, 1.19; 95%

Table 1. Trials Comparing Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers with Other Regimes in Hypertensive Patients*

Trial	Year	Type of Patients (n)	Years of Follow-up (n)	Drugs Compared	Entry BP (mm Hg)	BP Difference During Study	P	Primary Endpoint	Relative Risk	95% CI	Other Significant Outcome Differences	P
UKPDS ⁷	1998	Hypertensive (n = 758)	9	Captopril vs atenolol	159/93	NS	NA	Cli diab event Diabetes death Total mortality	1.1 1.27 1.14	0.86–1.41 0.82–1.97 0.81–1.61	None	NS NS NS
CAPPB ⁸	1999	Hypertensive (n = 10,985)	6.1	Captopril vs DIUs/ β-blockers	162/100	Captopril; BP higher 2/2	NA	MI, stroke, CV death	1.05	0.90–1.22	43% higher incidence of stroke in captopril group	.004
STOP-2 ⁹	1999	Hypertensive (n = 4418)	4.6	ACEIs vs conventional	194/98	NS	NA	CV death	1.01	0.84–1.22	None	NS
LIFE ¹⁰	2002	Hypertensive (n = 9193)	4.8	Losartan vs atenolol	174/98	Losartan; SBP lower 1.1	.017	CV death, stroke, MI [†]	0.87	0.77–0.98	25% stroke reduction in losartan group	.001
ALLHAT ¹¹	2002/2003	Hypertensive (n = 24,309)	4.9	Chlorthalidone vs lisinopril	146/84	Lisinopril SBP higher 2	<.001	Fatal CHD, nonfatal MI	0.99	0.91–1.08	Lisinopril group: 15% higher stroke 19% higher HF	.02 <.001
ANBP-2 ¹²	2003	(n = 26,083)	4.1	ACEIs vs DIUs	168/91	NS	NA	CVS event total mortality [‡]	0.89	0.79–1.00	In men, RR = 0.83 In women, RR = 0.98;	.02 .98
JMJC-B ¹³	2004	Hypertensive (n = 1650)	3	ACEIs vs nifedipine	145/82	ACEI BP higher 4/1	<.01	Cardiac event	1.05	0.81–1.37	ACEI group coronary lumen narrowed	NS
VALUE ¹⁴	2004	Hypertensive (n = 15,245)	4.2	Amlodipine vs valsartan	155/88	Valsartan BP higher 2.1/1.7	<.0001	CV event	1.04	0.94–1.15	Valsartan group 19% higher MI	.02

*Trials should show (1) no significant difference in primary endpoint in most studies and (2) the group with lower blood pressure had lower adverse clinical outcome regardless of strategy.

[†]P = .021.

[‡]P = .05.

Cli diab, clinical diabetes; DIUs, diuretics; ACEIs, angiotensin-converting enzyme inhibitors; NS, not significant; NA, not available; BP, blood pressure; MI, myocardial infarction; CV, cardiovascular; SBP, systolic blood pressure; CHD, coronary heart disease; UKPDS, United Kingdom Prospective Diabetes Study Group; CAPPB, Captopril Prevention Project; STOP-2, Swedish Trial in Old Patients with Hypertension 2; LIFE, Losartan Intervention For Endpoint Reduction in Hypertension Study; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ANBP-2, Second Australian National Blood Pressure Study Group; JMJC-B, Japan Multicenter Investigation for Cardiovascular Diseases-B randomized trial; VALUE, Valsartan Antihypertensive Long-Term Use Evaluation; RR, relative risk; HF, heart failure.

CI, 1.07–1.31); stroke (RR, 1.15; 95% CI, 1.02–1.30); and combined cardiovascular disease (RR, 1.10; 95% CI, 1.05–1.16). Subsequent analysis showed that these findings apply no matter the diabetic state, renal function status, or racial make-up of the patients studied.^{17–20} ALLHAT strongly suggests that lisinopril, an ACEI, has no special cardiovascular protective effect and actually may be inferior to the diuretic in preventing stroke and heart failure.^{21–24}

The ANBP2 study was interpreted as showing ACEIs to be better than the diuretic.¹² Unlike ALLHAT, which was a double-blind trial that followed a strict protocol of therapeutic intervention, ANBP2 was an open-labeled trial of patients randomized to ACEIs (n = 3044) or the diuretic (n = 3039); the choice of initiating dose and type of drug was left to the participating general practitioner. BP reduction was similar over 4.1 years and treatment with ACEIs resulted in a lower primary endpoint of cardiovascular events or total death that was of borderline significance (ACEIs, 22.8% and diuretic, 24.2%; RR, 0.89; 95% CI, 0.79–1.00). When considering only the female population (51% of total), there was no difference between the ACEI and diuretic groups (RR, 1.00; 95% CI, 0.83–1.22). Total mortality, coronary events, heart failure, and stroke were all similar in the 2 groups. Thus, ANBP2 actually confirms the results of ALLHAT by showing that ACEIs and diuretics are almost equivalent in reducing adverse cardiovascular events in hypertensive patients.

The JMIC-B trial randomized 1650 Japanese hypertensive patients with coronary artery disease to either nifedipine-retard or an ACEI.¹³ After 3 years, the primary endpoint comprising cardiac death, MI, angina, heart failure, hospitalization, and coronary intervention was equivalent on nifedipine-retard and ACEI (RR, 1.05; 95% CI, 0.81–1.37). Minimum coronary lumen diameter did not change with the use of CCBs but decreased significantly using ACEIs.²⁵ Thus, although JMIC-B showed no difference in clinical cardiovascular outcome between CCBs and ACEIs, it raised the possibility of an antiatherogenic effect with CCB treatment.

The idea that ACEIs may have cardiovascular-protective effects did not come from trials in hypertensive patients but from placebo-controlled trials in patients at high cardiovascular risk. However,

these trials have not produced consistent results and interpretation is controversial because patients who were treated always ended up with a lower BP compared with those in the placebo group (Table 2). HOPE recruited 9297 high-risk patients; 80% had coronary disease, 47% had hypertension, and 38% had diabetes.²⁶ They were randomized to ramipril 10 mg daily or placebo. After 5 years, the primary endpoint of MI, stroke, or cardiovascular death was significantly reduced with ramipril (14% vs 17.8%; RR, 0.78, 95% CI, 0.70–0.86). Measured BP was reduced by 3/3 mm Hg on ramipril; the HOPE authors argued that this small reduction in BP could not mathematically account for the highly significant cardiovascular outcome reduction. A Swedish HOPE center reported that, although office and daytime BP were only mildly lowered by ramipril, in their cohort the reduction of 24 hour ambulatory BP (10/4 mm Hg) and nighttime BP (17/8 mm Hg) was much larger.³² Patients in the HOPE trial were given ramipril at night and office measurement the following day underestimates the actual BP reduction. A prospective trial using ramipril 1.25 to 10 mg daily among 591 patients produced a mean BP reduction of 20/15 mm Hg over 8 weeks; 85% of patients having mild to moderate hypertension were successfully controlled using ramipril 2.5 to 5 mg daily in a retrospective review.^{33,34} Thus, it is likely that the 10 mg of ramipril used in the HOPE trial *did* produce a highly significant BP reduction, in keeping with the Swedish report; this could account for much of the benefit seen.

In EUROPA, 12,218 patients with coronary artery disease (27% were hypertensive, 12% were diabetic) were randomized to perindopril 8 mg daily or matching placebo.²⁸ BP was 9/4 mm Hg lower in patients in the perindopril treatment arm. After 4.2 years, the primary endpoint of cardiovascular death, MI, or cardiac arrest was 8% on perindopril and 10% on placebo (RR, 0.8; 95% CI, 0.71–0.91). As in the HOPE study, some have again attributed the clinical benefit with perindopril to the lower BP achieved.^{35,36} In PROGRESS, patients with a previous stroke or transient ischemic attack were randomized to active treatment (n = 3051) or placebo (n = 3054).²⁷ Active treatment was perindopril 4 mg, and indapamide was added at the discretion of the doctors. Overall, after a mean of 3.9 years treatment reduced BP by 9/4

Table 2. Trials Comparing Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers with Placebo in Patients at High Risk of Cardiovascular Events*

Trial	Year	Type of Patient (n)	Years of Follow-up (n)	ACEI Dosage	ARB Dosage	Entry BP (mm Hg)	Mean BP Reduction [†] (mm Hg)	Primary Endpoint	Relative Risk	95% CI	P
HOPE ²⁶	2000	High risk (n = 9297)	5	Ramipril, 10 mg		139/79	3/2 [§]	MI, stroke, CV death	0.78	0.70–0.86	<.001
PROGRESS ²⁷	2001	Stroke/TIA (n = 2561)	3.9	Perindopril, 4 mg		147/86	5/3	Stroke	0.95	0.81–1.23	NS
EUROPA ²⁸	2003	IHD (n = 12,218)	4.2	Perindopril, 8 mg		137/82	5/2	CV death, MI, cardiac arrest	0.80	0.71–0.91	.0003
CAMELOT ²⁹	2004	IHD (n = 1328)	2	Enalapril, 20 mg		129/78	6/3	CV events	0.85	0.67–1.07	NS
PEACE ³⁰	2004	IHD (n = 8290)	4.8	Trandolapril, 4 mg		133/78	3/1	CV death, MI, revascularization	0.96	0.88–1.06	NS
JIKEI ³¹	2007	High risk (n = 3081)	3.1		Valsartan, 40–160 mg	139/81	1/1	CV morbidity/mortality	0.61	0.47–0.79	.0002
TRANSCEND ³²	2008	High risk (n = 5926)	4.7		Telmisartan, 80 mg	141/82	4/2	CV death, MI, Stroke, CCF hospitalization	0.92	0.81–1.05	NS
PROFESS ³³	2008	Stroke (n = 20,332)	2.5		Telmisartan, 80 mg	144/84	4/2	Stroke	0.95	0.86–1.04	NS

*These trials do not consistently produce a significant reduction of clinical primary end point.

[†]As compared with placebo.

[‡]Results of patients only on perindopril (single drug) compared with placebo.

[§]HOPE substudy: Mean 24-hr BP reduction vs placebo, 10/4; P = .03. Mean nighttime BP reduction vs placebo, 17/8; P < .001.

^{||}Results of patients on enalapril compared with placebo.

[¶]Mean BP reduction vs placebo at 6 months, SBP 2.1 (P = .0005); DBP 2.1 (P < .0001). Mean BP reduction vs placebo at 1 year, SBP 1.5 (P = .0034); DBP 1.3 (P = .0003). TIA, transient ischemic attack; IHD, ischemic heart disease; ACEI, angiotensin-converting enzyme inhibitor; BP, blood pressure; MI, myocardial infarction; CV, cardiovascular; ARB, angiotensin receptor blocker; CCF, congestive cardiac failure; NS, not significant; HOPE, Heart Outcomes Prevention Evaluation; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; EUROPA, European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease; CAMELOT, Comparison of Armlodipine vs Enalapril to Limit Occurrences of Thrombosis Trial; PEACE, Prevention of Events with ACEIs Trial; JIKEI, Jikei Heart Study; TRANSCEND, Telmisartan Randomised Assessment Study in ACE-Intolerant Subjects with Cardiovascular Disease; PROFESS, Prevention Regimen for Effectively Avoiding Second Strokes Trial.

mm Hg and produced a significant reduction in the primary endpoint of total stroke (10% vs 14%; RR, 0.72; 95% CI, 0.62–0.83). Closer analysis of the data showed that patients treated only with the ACEI perindopril had a smaller BP reduction of 5/3 mm Hg and an insignificant reduction of stroke compared with placebo (RR, 0.95; 95% CI, 0.77–1.19). Addition of the diuretic indapamide produced a larger BP reduction (12/5 mm Hg) and resulted in a highly significant reduction in stroke (RR, 0.52; 95% CI, 0.46–0.70). Thus, rather than showing that perindopril had special value in stroke reduction, PROGRESS actually showed the value of aggressive BP reduction in preventing stroke among high-risk patients.^{37,38}

Two other trials, PEACE and CAMELOT, also suggest that ACEIs do not have any special cardiovascular protective effects. In PEACE, 8290 patients with stable coronary artery disease and normal left ventricular function were randomized to either trandolapril 4 mg daily or placebo; 45% had hypertension and 17% had diabetes.³⁰ Mean BP at entry was 133/78 mm Hg; by 36 months it was reduced by 4.4/3.6 mm Hg on ACEIs and by 1.4/2.4 mm Hg in the placebo group. After 4.8 years, the primary endpoint of nonfatal MI, cardiovascular death, or revascularization was not significantly different in the 2 groups (21.9% trandolapril, 22.5% on placebo; RR, 0.96; 95% CI, 0.88–1.06). Similarly there was no difference in the individual composite of the primary endpoint or in total mortality. Patients in PEACE were at lower cardiovascular risk than those in EUROPA or HOPE, with a higher proportion using lipid-lowering therapy (entry systolic BP, 139 mm Hg [HOPE], 137 mm Hg [EUROPA], 133 mm Hg [PEACE]; death from cardiovascular causes in placebo, 63% [HOPE], 59% [EUROPA], 47% [PEACE]; lipid-lowering therapy, 29% [HOPE], 56% [EUROPA], 72% [PEACE]). PEACE thus shows that, in low-risk coronary patients who are already on intensive risk factor management, the addition of an ACEI provides no further reduction in clinical cardiovascular outcome.

CAMELOT randomized 1991 high-risk patients with angiographic coronary disease and a diastolic blood pressure below 100 mm Hg to placebo, amlodipine, or enalapril.²⁹ From a baseline BP of 129/78 mm Hg, during 2 years BP increased 0.7/0.6 mm Hg with placebo, decreased 4.8/2.5

mm Hg on amlodipine, and decreased 4.9/2.4 mm Hg on enalapril. The primary cardiovascular endpoint was 23.1% with placebo, 16.6% with amlodipine (RR 0.69; 95% CI, 0.54–0.88) and 20.2% with enalapril (RR, 0.85; 95% CI, 0.67–1.07). CAMELOT thus suggests that the CCBs, not ACEIs, may have a special role in reducing cardiovascular clinical events in high-risk patients. Among CAMELOT patients with a systolic BP above the mean, intravascular ultrasound showed significantly less progression of coronary atherosclerosis in patients using amlodipine compared with placebo and no difference in the atherosclerotic progression between enalapril and placebo. As in JMIC-B, CAMELOT suggests it may be the CCBs, not ACEIs, that has a special role in reducing in coronary atheroma.

Do ARBs have Special Cardiovascular Protective Effects?

As in the case of ACEIs, trials assessing the role of ARBs in cardiovascular disease prevention can be divided into 2 groups: those comparing ARBs with other drugs in hypertensive patients and those comparing ARBs with placebos in patients at high cardiovascular risk (Tables 1 and 2).

LIFE randomized 9193 hypertensive patients with left ventricular hypertrophy to either losartan or atenolol.¹⁰ There was a marked reduction of stroke in the losartan group (5% vs 7%; RR, 0.87; 95% CI, 0.63–0.89), and this caused a significant reduction in the composite primary endpoint of death, MI, or stroke (11% vs 13%; RR, 0.87; 95% CI, 0.77–0.98). New-onset diabetes was lower in patients using losartan, suggesting that angiotensin antagonism has a favorable effect on glucose metabolism, a finding also noted with captopril in the CAPPP trial. When reviewing only the 1195 diabetic patients in LIFE,³⁹ the benefit of losartan was more remarkable, with a significant reduction not only in the primary endpoint (RR, 0.76; 95% CI, 0.58–0.98), but also in cardiovascular and total mortality. Surprisingly, stroke reduction with losartan was not statistically significant in this diabetic population (RR, 0.79; 95% CI, 0.55–1.14). The results of LIFE should be read together with data from other trials. ACEIs were weaker than the comparator drug in preventing stroke in both CAPPP and ALLHAT.^{8,11} Only approximately 10% of patients were on monotherapy with losar-

tan or atenolol at the end of the LIFE trial; thus it is misleading to solely attribute the better clinical outcome to the superiority of losartan over atenolol when so few patients were actually on monotherapy.⁴⁰ The mean systolic BP was lower in patients on losartan in both the overall (1.1 mm Hg; $P = .017$) and diabetic (2 mm Hg; P not stated) patients, making it possible that the benefit resulted from better BP reduction on the losartan arm. Furthermore, recent reports suggest that β -blockers, especially atenolol, may be less useful in older hypertensive patients and are specially weak in preventing stroke.^{41–43} LIFE actually shows the importance of BP reduction and the weaker efficacy of atenolol in stroke prevention, not a special cardiovascular protective effect with losartan.

The VALUE trial randomized 15,245 hypertensive patients to either valsartan or amlodipine.^{14,44} Attained BP was significantly lower with amlodipine. After 4.2 years there was no difference in the primary endpoint of first cardiac event (RR, 1.04; 95% CI, 0.94–1.15). Although the occurrence of new diabetes was lower among patients using valsartan (RR, 0.77; 95% CI, 0.69–0.86), incidence of MI was higher among patients using the ARB (RR, 1.19; 95% CI, 1.02–1.38). However, after correction for the BP difference, MI incidence was similar in the 2 groups (RR, 0.97; 95% CI, 0.80–1.19).⁴⁵ Patients reaching adequate BP control by 6 months were shown to fare better, regardless of drug type used. The benefit of good BP control is thus more important than the subtle differences between antihypertensive drugs. A better metabolic profile in the ARB arm did not translate into a reduction in adverse outcome. The VALUE trial, as does ALLHAT, suggests that drugs targeting the renin-angiotensin system do not have special cardiovascular protective effects despite producing a better metabolic profile; they also seem less efficacious in reducing BP compared with CCBs and diuretics.¹⁶

The JIKEI Heart Study randomized 3081 high-risk patients with cardiovascular disease to valsartan 40 to 160 mg daily or other treatment that excludes ARBs.³¹ After 3.1 years, the primary endpoint of cardiovascular mortality and morbidity was significantly lower with valsartan (RR, 0.61; 95% CI, 0.47–0.79), driven by lower stroke and transient ischemic attack (RR, 0.60; 95% CI, 0.38–0.95), angina (RR, 0.35; 95% CI, 0.20–0.58), and heart

failure (RR, 0.53; 95% CI, 0.31–0.94). Although mean initial (139/81 mm Hg) and final (132/77 mm Hg) BPs were reported to be similar to those in patients in the valsartan and placebo groups, at 6 months BP was 2/2 mm Hg lower in the patients treated with the ARB. In the VALUE trial, patients reaching a lower BP at 6 months had fewer clinical events, regardless of the antihypertensive drug used.⁴⁵ It is thus debatable whether the reduction in clinical outcome in the JIKEI study is because of a beneficial effect of valsartan or the better BP levels achieved.⁴⁶

The Telmisartan Randomised Assessment Study in ACE-Intolerant Subjects with Cardiovascular Disease (TRANSCEND) trial randomized 5926 patients intolerant of ACEIs who had prior cardiovascular disease or diabetes with end-organ damage to either telmisartan 80 mg daily or placebo.⁴⁷ Mean follow-up was 56 months. Although BP was lower by 4.0/2.2 mm Hg in the telmisartan group, the primary composite outcome (cardiac death, MI, stroke, or hospitalization for heart failure) was similar in the 2 groups (15.7% telmisartan, 17% placebo; RR, 0.92; 95% CI, 0.81–1.05). The reduction in secondary outcome (cardiac death, MI, or stroke) was of borderline significance (RR, 0.87; 95% CI, 0.76–1.00). TRANSCEND thus does not strongly suggest a cardiovascular protective role for the ARBs. In the Prevention Regimen for Effectively Avoiding Second Strokes Trial (PROFESS), 20,332 patients who had recently had an ischemic stroke were randomized to either telmisartan 80 mg or placebo and followed for a mean of 2.5 years.⁴⁸ Although the BP was 3.8/2.0 mm Hg lower in the telmisartan group, the primary endpoint of recurrent stroke was not significantly reduced (8.7% telmisartan, 9.2% placebo; RR, 0.95; 95% CI, 0.86–1.04). Major cardiovascular events (RR, 0.94; 95% CI, 0.87–1.01), and new diabetes (RR, 0.82; 95% CI, 0.65–1.04) were also not significantly altered. It is interesting to compare how strikingly similar the results of PROFESS are to those of PROGRESS.²⁷ In PROGRESS, among patients only on perindopril the BP reduction was 5/3 mm Hg, with reduction of stroke (RR, 0.95) and major vascular event (RR, 0.96) not significantly different from placebo. In PROFESS, the BP reduction of 3.8/2.0 mm Hg produced a non-significant reduction of stroke (RR, 0.95) and cardiovascular event (RR, 0.94). Thus, PROFESS

Table 3. Discontinuation Rate of Antihypertensive Drugs in the Comparative Trials

Trial	Antihypertensive Drug Class (%)					DIU
	ACEI	ARB	ACEI + ARB	BB	CCB	
ONTARGET (n = 25,620)	25	23	29			
LIFE (n = 9193)		23		27		
VALUE (n = 15,245)		26			24	
ALLHAT (n = 24,309)	27				20	20
UKPDS (n = 758)	22			35		
JMIC-B (n = 1650)	9				5	

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DIU, diuretic; BB, β -blocker; ONTARGET, Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; LIFE, Losartan Intervention For Endpoint Reduction in Hypertension Study; VALUE, Valsartan Antihypertensive Long-Term Use Evaluation; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; UKPDS, United Kingdom Prospective Diabetes Study Group; JMIB-B, Japan Multicenter Investigation for Cardiovascular Diseases-B randomized trial.

confirms the impression of PROGRESS that the rennin-angiotensin antagonists do not have a special stroke-reducing or cardiovascular-preventive effect.

What is the Lesson from ONTARGET?

The ONTARGET trial sought to answer 2 questions: whether ARBs are similar to ACEIs in therapeutic efficacy and whether their combination could produce even better clinical results.⁴⁹ Patients with vascular disease or diabetes were randomized to 10 mg ramipril (n = 8576), 80 mg telmisartan (n = 8542), or both (n = 8502). From the same initial level of 142/82 mm Hg, after 6 weeks BP fell to 135/78 mm Hg on ramipril, 134/77 mm Hg on telmisartan, and 132/76 mm Hg on combination therapy. The primary endpoint was a composite of cardiovascular death, MI, stroke, or hospitalization for heart failure. After a median of 56 months, compared with ramipril there was no difference in the primary endpoint with telmisartan (RR, 1.01; 95% CI, 0.94–1.09) or combination therapy (RR, 0.99; 95% CI, 0.92–1.07). ONTARGET thus showed that ARBs and ACEIs are equivalent in their clinical efficacy. The absence of any reduction in cardiovascular outcome from the ACEI and ARB combination arm is also another piece of evidence suggesting that antagonizing the rennin-angiotensin system does not produce any special cardiovascular-protective effect.

Although adverse effects and discontinuation rates were lower with telmisartan compared with ramipril, the discontinuation rate with telmisartan of 23% is a reminder that ARBs are not free of adverse effects. In fact, reviewing the discontinua-

tion rates in drug trials of hypertensive patients suggest that the CCBs and diuretics actually may be best when seeking to lower discontinuation and enhance compliance (Table 3). Although the combination of ramipril and telmisartan better reduced proteinuria compared with ramipril alone, major renal outcomes (need for dialysis, doubling of serum creatinine, and death) were surprising higher in the combination group (14.5% vs 13.5%; RR, 1.09; 95% CI, 1.01–1.18).⁵⁰ Furthermore, adverse side effects were highest with combination therapy. Thus, it may be that patients respond best when different strategies are used for treatment, and excessively targeting a single pathway will result in less clinical benefit with higher risk of adverse consequences.

Conclusion

It is hard to escape the conclusion that the rennin-angiotensin antagonists do not show special cardiovascular-protective properties and that there are no major differences between the different antihypertensive drugs in their ability to reduce adverse cardiovascular outcomes.⁵¹ There was no significant difference in the cardiovascular primary endpoint in most of the comparative drug trials done among hypertensive patients (Table 1). In CAPPP (captopril vs β -blocker/diuretic); ALLHAT (doxazosin, amlodipine, lisinopril vs chlorthalidone); LIFE (losartan vs atenolol); and VALUE (amlodipine vs valsartan), where a major cardiovascular endpoint was reduced in one of the treatment arms, it was always the arm with the lower achieved BP that saw the better clinical outcome.^{8,10,11,14,16,39} Thus, in-

stead of trying to work out why the angiotensin antagonists could be cardioprotective in some trials (LIFE) but not in others (CAPPP, ALLHAT, VALUE), the simple and consistent message is that the lower the achieved BP the lower the adverse cardiovascular outcome in hypertensive patients.

The absence of a cardioprotective effect with the angiotensin antagonist is reinforced by the inconsistent results of trials comparing ACEIs and ARBs with placebo in patients at high risk for cardiovascular events (Table 2). HOPE, EUROPA, and the JIKEI Heart Study showed significant reduction of cardiac outcomes, whereas PROGRESS, PEACE, CAMELOT, TRANSCEND, and PROFESS did not.^{26–31,47,48} In CAMELOT, compared with the placebo group cardiovascular outcome was not affected by enalapril but was significantly lower in patients using amlodipine.²⁹ Furthermore, progression of coronary atherosclerosis was retarded with amlodipine but showed no difference between the enalapril and placebo groups. Thus rather than the ACEIs, it may be the CCBs that have an antiatherosclerotic effect.

The case against the angiotensin antagonists having a special cardiovascular protective effect is strongly supported by the results from ONTARGET. This study showed that combining ARBs with ACEIs, each at half of the maximal doses, resulted in a lower BP, did not lower cardiovascular outcome, and produced a higher incidence of renal and other adverse events.^{49,50} If ACEIs and ARBs are especially useful in protecting against cardiac disease, then logically the combination of ARBs with ACEIs should further lower cardiovascular outcomes. This absence of a reduction in cardiovascular outcome from the ACEI and ARB combination arm in ONTARGET is further evidence that suggests that these drugs do not have any special cardiovascular-protective effect.

The higher incidence of adverse events with combination therapy in ONTARGET emphasizes the point that ARBs and ACEIs are not free of side effects (Table 3). In ALLHAT, the discontinuation rate of patients using ACEIs was higher than that in those using a diuretic, whereas in VALUE the incidence of dizziness, headache, angina, diarrhea, and syncope were all significantly higher in patients using ARBs compared with those using CCBs.^{11,14} Clinicians initiating patients onto ARB or ACEI treatment must be aware of these potential adverse

effects, which may reduce compliance during long-term maintenance therapy.

Finally, it is interesting to consider what target BP to aim for when seeking to reduce cardiovascular outcomes in high-risk patients. In PEACE, the BP at trial initiation was 135/78 mm Hg; treatment with trandolapril lowered BP but did not reduce cardiovascular events.³⁰ In ONTARGET, the ramipril group was treated to a BP of 133/78 mm Hg; telmisartan or combination therapy lowered BP further but did not further reduce clinical cardiovascular outcomes.⁴⁹ Thus, 135/80 mm Hg represents a reasonable target when seeking to reduce cardiovascular outcomes. The hypertension guidelines all define normal BP to be <135/80 mm Hg, although optimal BP is said to be <120/80 mm Hg.^{52–55} Although epidemiologic reviews suggest that the lowest risk of cardiovascular disease occur at a systolic BP of <120 mm Hg, further clinical trials are needed to decide if pharmacological treatment to below the normal BP of 135/80 mm Hg produces clinical benefit.^{56–59} It is important to also remember that all cardiovascular risk factors require appropriate management.⁶⁰ Just as ONTARGET showed that increasingly attacking the angiotensin pathway did not bring increasing clinical benefit, when seeking to reduce cardiovascular outcome it may be more fruitful to target different pathologic processes and risk factors instead of just concentrating on reducing BP levels.⁶¹

Treatment Recommendations

(1) For hypertensive patients, ACEIs and ARBs are equivalent but not superior to other antihypertensive drugs in their cardiovascular protective effects (GRADE A), and clinical cardiovascular outcomes will be reduced with tight BP control (GRADE A).

(2) For patients with normal left ventricular function who are at high risk of cardiovascular events, ACEIs and ARBs do not exert special cardiovascular-protective effects additive to their antihypertensive action (GRADE B), and clinical cardiovascular outcome is best reduced by treatment of all risk factors, including normalizing BP levels (to <135/80 mm Hg) and not by adding ACEIs/ARBs to every patient's treatment (GRADE B).

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