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Scientific Update™

ACEI and ARB: Balancing the hope, hype, and evidence

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Angiotensin II plays a key role in the promotion of endothelial dysfunction and the development of atherosclerosis. Both angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) have the potential to reduce the adverse effects of angiotensin II in the arterial wall. However, despite the proven benefits of ACE inhibitors for vascular protection, following myocardial infarction (MI) and in heart failure, no consistent evidence supports the use of ARBs in these clinical settings. It is possible that the enhancement of bradykinin with ACE inhibition helps to restore endothelial function and hence has additive benefits compared to the ARBs.

Endothelial dysfunction, angiotensin, and atherosclerosis

The vascular endothelium regulates vascular homeostasis and maintains the integrity of the arterial wall. When endothelial dysfunction develops, the balance shifts towards vasoconstriction, a prothrombotic and proinflammatory milieu, and promotion of cell proliferation. The development and complications of atherosclerosis are promoted by an inflammatory response, which is initiated by endothelial dysfunction.[1] Angiotensin II is a key molecule in the promotion of inflammation through NFκB activation to induce cytokines (eg, IL-6) and adhesion molecules (eg, VCAM-1 and MCP-1) that encourage monocyte adhesion and migration into the vessel wall. Angiotensin II also promotes the formation of oxygen-free radicals that further increase the inflammatory response. A vicious cycle is created as inflammatory cells synthesize enzymes, which further increase angiotensin II synthesis.[2]

Angiotensin II can also result in the synthesis of oxygen-free radicals by interfering with nitric oxide (NO) synthesis.[3] NO is synthesized from L-arginine by the enzyme NO synthetase using the cofactor tetrahydrobiopterin (BH4). Angiotensin quenches BH4, resulting in the same enzyme system generating highly reactive oxygen species rather than NO.

ACE inhibitors, ARBs and vascular disease

Angiotensin-converting enzyme (ACE) transforms angiotensin I to the active peptide angiotensin II. However, the same enzyme is responsible for the breakdown of bradykinin to inactive peptides. Inhibition of ACE not only reduces angiotensin II levels, but also increases the availability of bradykinin, a mediator that promotes the synthesis of NO (Figure 1). This mechanism appears to be an important component of the ACE-inhibitor-induced improvement of endothelial function in coronary circulation, yet may be less important in the kidney. This differential effect of bradykinin on endothelial function may explain the different clinical trial outcomes of ACE inhibitors and ARBs on renal and cardiac endpoints.

Thus, the potential mechanisms for ACE-inhibitor mediated improvement of endothelial function are:

- decreased oxygen-free radical production
- increased NO synthesis
- increased bradykinin availability
- decreased cell adhesion molecules, such as VCAM-1 and MCP-1, which initiate inflammation.

ARBs have a potentially greater inhibitory effect on angiotensin II events mediated via the AT1 receptor. However, ACE inhibition results in additional benefits due to enhanced bradykinin availability. Animal models of arterial injury have shown the importance of bradykinin-mediated effects with ACE inhibition. ACE inhibition with ramipril had the greatest inhibitory effect on neo-intimal and medial proliferation. The combination of ramipril and the bradykinin inhibitor, HOE 140, reduced the inhibitory effect of ramipril by almost 50% to the level of benefit observed with the ARB, losartan.[4] Flow-mediated arterial dilatation in human radial arteries is enhanced by the ACE inhibitor, quinapril, an effect that is inhibited by the bradykinin B2 receptor blocker, icatibant.[5] These studies support the role of bradykinin in the mechanism of ACE-inhibitor-induced enhancement of endothelial function.

ACE inhibitors for cardiovascular protection

ACE inhibitors were initially introduced for the management of hypertension and as "vasodilators" for the treatment of heart failure.

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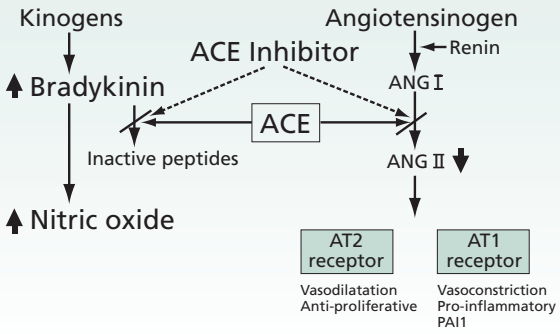
Figure 1: Angiotensin-converting enzyme (ACE) inhibition reduces angiotensin II (ANG II) and increases bradykinin



Clinical trials demonstrated that ACE inhibition reduced heart failure mortality, hospitalization for heart failure, and the development of heart failure in patients with ventricular dysfunction. Studies that observed subjects for more than 3 years (SOLVD[7,8] and SAVE[8,9] trials) showed a consistent reduction of MI during the period of treatment. Trials with shorter duration of treatment such as AIRE[10,11] and TRACE[13] showed a nonsignificant trend toward less MI. These trials led to the rationale for studies to evaluate whether ACE inhibition reduces vascular events in patients at risk, yet without heart failure or important left ventricular dysfunction. The QUIET study,[13] using quinapril, demonstrated a nonsignificant trend toward fewer vascular events. However, the trial was grossly underpowered (1,750 patients) and the treatment period was <2 years.

The HOPE study[14] was carried out at 267 centres in 19 countries over 3 continents, and enrolled 9,297 high-risk patients with a history of coronary disease, stroke, peripheral vascular disease, or diabetes, with at least 1 risk factor for vascular disease. The subjects were >55 years old, had no history of heart failure, recent MI or stroke, and when known, a left ventricular ejection fraction >40%. Eligible patients were randomized to either ramipril 10 mg daily or placebo. During the 4.5-year follow-up period, ramipril-treated patients had 22% less cardiovascular death, MI, or stroke. Similar benefits were observed in a wide range of patient groups (Figure 2). Those enrolled with or without cardiovascular disease, diabetes, hypertension, prior MI, cerebrovascular disease, or peripheral vascular disease had a similar 20% to 25% reductions in vascular events. Each of the components of the primary endpoint (CVD death, stroke, MI) was significantly reduced. In addition, there was a 32% reduction in the incidence of new diabetes. These benefits are summarized by the treatment effect for 1,000 patients receiving ramipril 10 mg daily for 4 years; treatment will prevent 20 deaths, 24 MIs, 23 revascularizations, or 150 events in 70 patients.

The results of on-going trials such as PEACE, EUROPA, and IMAGINE are awaited to confirm the value of ACE inhibitors for vascular protection. However, ACE inhibitors are first-line treatment for patients with, or at high risk for, vascular disease in the current recommendations of the AHA/ACC, the American Diabetic Association, and the Canadian Hypertensive Society.

ARBs and vascular protection

Clinical trials examining the benefits of ARBs have focused on patients with hypertension, heart failure, and renal dysfunction (Table 1) and few have had sufficient power to show any impact on vasculoprotection.

Figure 2: The beneficial effect of treatment with ramipril on the composite outcome of myocardial infarction, stroke, or death from cardiovascular causes overall and in various predefined subgroups.[14]

	No. of Patients	Incidence of Composite Outcome in Placebo Group
Overall	9,297	17.8
Cardiovascular disease	8,162	18.7
No cardiovascular disease	1,135	10.2
Diabetes	3,577	19.8
No diabetes	5,720	16.5
Age <65 yr	4,169	14.2
Age ≥65 yr	5,128	20.7
Male sex	6,817	18.7
Female sex	2,480	14.4
Hypertension	4,355	19.5
No hypertension	4,942	16.3
History of coronary artery disease	7,477	18.6
No history of coronary artery disease	1,820	14.2
Prior myocardial infarction	4,892	20.9
No prior myocardial infarction	4,405	14.2
Cerebrovascular disease	1,013	25.9
No cerebrovascular disease	8,284	16.7
Peripheral vascular disease	4,051	22.0
No peripheral vascular disease	5,246	14.3
Microalbuminuria	1,956	26.4
No microalbuminuria	7,341	15.4

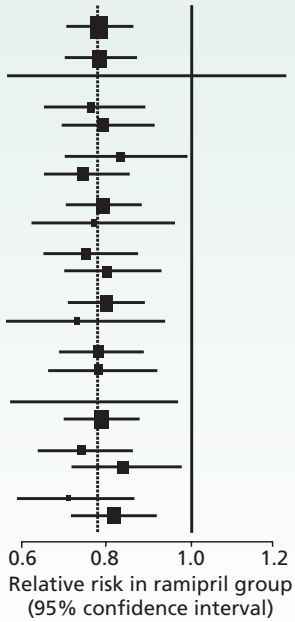


Table 1: Completed and on-going major clinical trials of angiotensin receptor blockers in cardiovascular disease (other than BP-lowering trials)

Trial	N	Agent	Target	End-points
LIFE[15]	9,193	Losartan vs. atenolol	Hypertension with LVH	CV events, regression LVH
Val-HeFT[16]	5,010	Valsartan vs. placebo	Heart failure	
ELITE 2[17]	5,100	Losartan vs. captopril	Heart failure	All-cause mortality
CHARM[18]**		Candesartan	Heart failure	
OPTIMAAL[19]	5,477	Losartan vs. captopril	MI + LV dysfunction + CHF	Mortality, CV events
IRMA 2[20]		Irbesartan vs. placebo	Microalbuminura	Development of nephropathy
IDNT[21]		Irbesartan vs. placebo or amlodipine	Proteinuria	Progression of renal disease
RENAAL[22]	1,513	Losartan vs. placebo	Proteinuria	Progression of renal disease
VALUE*	14,400	Valsartan vs. amlodipine	High-risk hypertension	CV events
SCOPE*	4,000	Candesartan vs. placebo	Elderly	Cognitive function, CV events
VALIANT*	14,500	Valsartan vs. captopril vs. both	Post-MI CHF	Mortality
ONTARGET*	>20,000	Telmisartan vs. ramipril vs. both	High-risk hypertension	CV events

* On-going clinical trials ** Partially reported trial

Hypertension

The LIFE trial[15] compared losartan with atenolol in 9,193 subjects 55- to 80-years-old, with moderately severe hypertension and ECG evidence of left ventricular hypertrophy (LVH). Over the 5-year treatment period, patients receiving losartan had a 13% reduction in the primary composite endpoint of CV mortality, MI, and stroke. However, the composite endpoint was reduced entirely by a 25% reduction in stroke, with no hint of any reduction of MI, and a non-significant 11% reduction of CV mortality. Fewer new onset diabetics (-25%) were observed in the losartan group compared to the atenolol-treated group. Since blood pressure reduction was similar in both groups, it is claimed that the reduction of CV events is due to the vascular-protective properties of the ARB losartan. Although possible, it is surprising that a consistent reduction of other vascular events such as MI was not observed. Furthermore, the study compared losartan to a beta-blocker, which is not effective for LVH regression and also not recommended for treatment of the elderly hypertensive population enrolled in the LIFE trial. Finally, the results of the LIFE trial are not widely applicable, since only a small proportion of hypertensive patients have ECG criteria for LVH.

Post-myocardial infarction

The OPTIMAAL trial[19] enrolled 5,477 patients with MI and symptomatic heart failure or LV dysfunction to randomized treatment with losartan 50 mg daily or captopril 50 mg tid. All-cause mortality, the primary end-point, tended to be lower in the captopril-treated patients (losartan 18.2%, captopril 16.4%, $P=0.069$), and CV mortality was significantly less (losartan 15.3%, captopril 13.3%, $P=0.032$). There was no difference for re-infarction or stroke between the treatment groups. This clearly negative trial may have suffered from inadequate losartan dosage. However, the results do not encourage the use of ARBs as a replacement for ACE inhibitors in patients following MI.

Heart failure

A recent meta-analysis[23] concluded it could not confirm that ARBs were superior to ACE inhibitors in patients with heart failure for the reduction of all-cause mortality or heart failure hospitalization. The meta-analysis of 7 small trials that compared ARBs with placebo in 2,259 patients showed the direction of benefit was in favour of the ARBs. No trial demonstrated a reduction in MI as observed in the ACE inhibitor trials described above. Can it be inferred that ARBs are as good as ACE inhibitors for the management of heart failure? Since the trials were designed as superiority trials, equivalence cannot be established from the current data.

Nephroprotection

The nephroprotective benefits of the ARBs, irbesartan and losartan, were compared with placebo in the IRMA 2,[20] IDNT,[21] and RENAAL[22] studies. The studies demonstrated that ARBs retard the progression of diabetic nephropathy from both the early stages of microalbuminuria and the more advanced stage of nephropathy with overt proteinuria. However, despite nephroprotection, a high proportion of patients died. In the RENAAL[22] study, the combined end-point (doubling of serum creatinine, end-stage renal disease, or death) was reduced by losartan (losartan 43.5%, placebo 47.1%, $P=0.02$), yet there was no reduction in death (losartan 21%, placebo 20.3%, ns). For high-risk patients with diabetic nephropathy, ARBs have no proven cardiac-protective benefits.

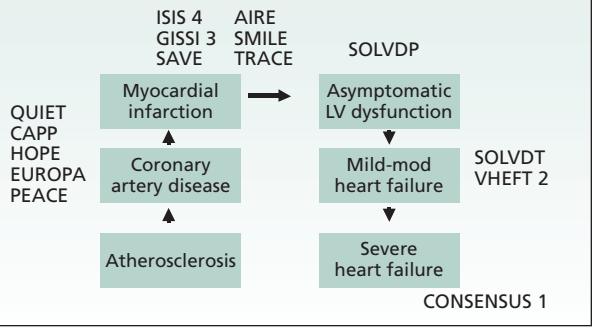
Vascular protection in the high-risk patient with diabetes

Cardiovascular disease accounts for >70% of mortality in the diabetic population. The diabetic patient has a similar risk of death, MI, or stroke as a nondiabetic patient who has already had a MI or stroke. There is a progressive increase in cardiovascular mortality with the development of nephropathy: patients with microalbuminuria have a 10%, 3-year mortality, whereas with end-stage renal disease there is a 50%, 3-year mortality.

The MICRO-HOPE trial[24] demonstrated the enhanced benefit of ACE inhibition in diabetic patients with large reductions of each of the components of the primary end-point (MI, 22%, $P=0.01$; stroke, 33%, $P=0.007$; CV death, 37%, $P=0.0001$). In addition, the development of overt nephropathy was reduced 24% ($P=0.027$) and the progression of proteinuria significantly retarded. In this population, only 0.5% of patients developed end-stage renal disease.

Analysis of the 1,195 diabetic patients in the LIFE trial[25] showed the losartan group had a 24.5% reduction in cardiovascular mortality compared with the atenolol-treated subjects. However, neither MI nor stroke was reduced by losartan. Furthermore, the LIFE study group of moderately severe hypertensive diabetic patients with ECG evidence

Figure 3: Clinical trials of ACE Inhibition have shown benefits with reduction of cardiovascular events at all stages in the coronary heart disease cycle



of LVH is not the diabetic population most commonly encountered, and severely limits the general applicability of the observation.

Diabetic patients in the HOPE study[24] were 40 times more likely to have either MI, stroke, or cardiovascular death, than to develop end-stage renal disease. Hence, a primary management goal in these high-risk patients is to prevent fatal and nonfatal vascular events. For patients with early diabetic nephropathy, the HOPE study demonstrates a high degree of vascular protection. Less robust evidence of both vascular and nephroprotection from ACE inhibitors is available for patients with more overt renal disease. The Captopril Study showed a 50% reduction in the development of end-stage renal disease or death in 409 patients with type I insulin-dependent diabetes with overt nephropathy.

Conclusions

Angiotensin plays a pivotal role in the development of atherosclerosis and the subsequent complications that result in the clinical presentations of MI, stroke and cardiovascular death. Angiotensin inhibitors have been shown in multiple clinical trials to reduce heart attack and stroke at all stages of the atherosclerotic heart disease cycle from the asymptomatic phase through to severe heart failure (Figure 3). In contrast, the ARBs, whilst having important antihypertensive and nephroprotective properties, have no consistent or proven vascular-protective benefits in this high-risk population. As a result, ACE inhibitors should be strongly considered for cardiovascular protection in high-risk patients, just as we consider lipid-lowering today. ARBs are a useful adjunct for enhanced blood pressure control, especially in the diabetic patient with nephropathy. For patients with heart failure who are intolerant of ACE inhibitors, an ARB may be used with some confidence. However, there is no evidence to support the claim that ARBs are a replacement for ACE inhibitors, especially for vascular protection.

References

1. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002;105: 1135-1143.
2. Dzau VJ. Theodore Cooper Lecture: Tissue angiotensin and pathobiology of vascular disease: a unifying hypothesis. *Hypertension* 2001;37:1047-1052.
3. Spieker LE, Luscher TF, Noll G. Current strategies and perspectives for correcting endothelial dysfunction in atherosclerosis. *J Cardiovasc Pharmacol* 2001;38 Suppl 2: S35-S41.
4. Farhy RD, Carretero OA, Ho KL, et al. Role of kinins and nitric oxide in the effects of angiotensin-converting enzyme inhibitors on neointima formation. *Circ Res* 1993;72: 1202-1210.
5. Hornig B, Kohler C, Drexler H. Role of bradykinin in mediating vascular effects of angiotensin-converting enzyme inhibitors in humans. *Circulation* 1997;95:1115-1118.
6. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigators. *N Engl J Med* 1992;327:685-691.
7. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med* 1991;325:293-302.
8. Rutherford JD, Pfeffer MA, Moye LA, et al. Effects of captopril on ischemic events after myocardial infarction. Results of the Survival and Ventricular Enlargement trial. SAVE Investigators. *Circulation* 1994;90:1731-1738.
9. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992;327:669-677.
10. Cleland JG, Erhardt L, Murray G, et al. Effect of ramipril on morbidity and mode of death among survivors of acute myocardial infarction with clinical evidence of heart failure. A report from the AIRE Study Investigators. *Eur Heart J* 1997;18:41-51.
11. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. *Lancet* 1993;342:821-828.
12. Kober L, Torp P, Carlsen JE, et al. A clinical trial of the angiotensin-converting enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. *N Engl J Med* 1995;333: 1670-1676.
13. Pitt B, Neill B, Feldman R, et al. The QUinapril Ischemic Event Trial (QUIET): evaluation of chronic ACE inhibitor therapy in patients with ischemic heart disease and preserved left ventricular function. *Am J Cardiol* 2001;87:1058-1063.
14. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;342:145-153.
15. Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002;359:995-1003.
16. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345:1667-1675.
17. Pitt B, Poole W, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000;355:1582-1587.
18. Granger CB, Ertl G, Kuch J, et al. Randomized trial of candesartan cilexetil in the treatment of patients with congestive heart failure and a history of intolerance to angiotensin-converting enzyme inhibitors. *Am Heart J* 2000;139:609-617.
19. Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. *Lancet* 2002;360:752-760.
20. Parving HH, Lehnert H, Brochner M, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001;345:870-878.
21. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;345:851-860.
22. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;345:861-869.
23. Jong P, Demers C, McKelvie RS, et al. Angiotensin-receptor blockers in heart failure: meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2002;39:463-470.
24. Gerstein HC, Bosch J, Pogue J, et al. Rationale and design of a large study to evaluate the renal and cardiovascular effects of an ACE inhibitor and vitamin E in high-risk patients with diabetes. The MICRO-HOPE Study. Microalbuminuria, cardiovascular, and renal outcomes. Heart Outcomes Prevention Evaluation. *Diabetes Care* 1996;19: 1225-1228.
25. Lindholm LH, Ibsen H, Dahlof B, et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002;359:1004-1010.

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