

Angiotensin-converting enzyme inhibitors: An ACE in the hole for everyone?

Numerous trials have confirmed that patients with hypertension and other compelling indications (heart failure, diabetes, stroke, and myocardial infarction) can benefit from first-line therapy with ACEIs.

ABSTRACT: Angiotensin-converting enzyme inhibitors (ACEIs) are commonly used to treat cardiovascular disorders. The use of ACEIs for hypertension is well established, although these agents have not proven to be superior to other antihypertensive agents. The use of ACEIs in heart failure is also well established, and has proven to reduce morbidity and mortality. ACEIs are now routinely used in myocardial infarction patients to reduce reinfarction and mortality risk, and are combined with a diuretic for secondary prevention in stroke patients. Proof that ACEIs also reduce the progression of diabetic nephropathy supports their use in all diabetic patients. With the evidence of efficacy now available, angiotensin-converting enzyme inhibitors should be considered for all patients with diabetes or a history of cardiovascular disease, except for those at low risk.

The use of angiotensin-converting enzyme inhibitors (ACEIs) is ubiquitous in the treatment of cardiovascular disorders. These agents inhibit the action of the angiotensin-converting enzyme that catalyzes the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. Inhibition of angiotensin II results in vasodilation, reduced sodium retention, and reduced sympathetic and renin-angiotensin-aldosterone system activation. There is considerable evidence available supporting the use of ACEIs in patients with hypertension, heart failure, and myocardial infarction (MI), and for prevention of secondary stroke, cardiovascular events, and diabetic nephropathy. ACEIs are considered contraindicated in patients with hyperkalemia, previous angioedema with ACEIs, pregnant patients, and patients with bilateral renal artery stenosis.

Hypertension

Several clinical trials have shown that ACEIs are effective agents in the treatment of hypertension; however, these trials have not shown ACEIs to be superior to other antihypertensives in the absence of compelling indications

(e.g., heart failure, diabetes, myocardial infarction). Three large, landmark studies investigating ACEI use in hypertension are the ALLHAT, the CAPPP trial, and the UKPDS.¹⁻³ The ALLHAT compared lisinopril with conventional therapy (chlorthalidone or amlodipine). The CAPPP trial compared captopril with conventional therapy (beta-blocker or diuretic), while the UKPDS compared captopril with atenolol. All three trials concluded that ACEIs are not superior to conventional therapy designed to treat uncomplicated hypertension in order to reduce risk of myocardial infarction, stroke, or cardiac death. Thus, for uncomplicated hypertension, an ACEI is one option among the various antihypertensive drug classes. If hypertension is accompanied by other compelling indications (previous stroke, diabetes, heart failure, myocardial infarction), then an ACEI is strongly recommended as the first-line antihypertensive therapy. This is support-

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ed by the most recent Joint National Committee hypertension guidelines (JNC 7 report) as well as by the 2010 Canadian Hypertension Education Program (CHEP) guidelines.^{4,5}

Heart failure

Clinical trials uniformly show that ACEIs reduce all-cause mortality in patients with varying degrees of heart failure. The initial trials of ACEI use in heart failure patients consistently showed significant reduction in mortality.^{6,7} More recent trials (the AIRE and TRACE studies) have also shown mortality reduction with ramipril and trandolapril.^{8,9} These landmark trials all demonstrated a mortality reduction with ACEI use when compared with placebo. The 2009 American College of Cardiology/American Heart Association (ACC/AHA) guidelines and 2006 Canadian consensus guidelines strongly recommend ACEI use in all heart failure patients with a reduced left ventricular ejection fraction (LVEF) of 40% or less to reduce mortality and worsening heart function.^{10,11} Current guidelines recommend the uptitration of an ACEI to achieve target doses or the highest dose tolerated by the patient. Optimal dosing of an ACEI in heart failure patients has been associated with decreased risk of hospitalization.

Myocardial infarction

Several studies demonstrate that the use of an ACEI in patients recovering from an MI results in a significant reduction in all-cause mortality and morbidity. Landmark trials (CCS-1, GISSI-3, and SMILE) all uniformly demonstrated a mortality reduction when ACEI therapy was used after an MI.¹²⁻¹⁴ More recent trials (the TRACE and AIRE studies) also demonstrated mortality reduction with ACEI use, particularly in patients with left ventricular dysfunction.^{8,9} A meta-

analysis of all published, major trials investigating the use of an ACEI after an MI conclusively supports a role for ACEI therapy in the early phase and ongoing management of MI.¹⁵ The 2004 ACC/AHA guidelines for ST-elevation MI strongly recommend the use of an ACEI for all patients to reduce mortality.¹⁶ However, for low-risk MI patients, the use of an ACEI is also reasonable and may be considered.¹⁷

Secondary stroke prevention

There have been only two studies investigating the role of an ACEI in secondary stroke prevention. The PROGRESS trial compared the use of perindopril and indapamide (in combination) versus perindopril alone versus placebo in patients with a history of stroke or transient ischemic attack.¹⁸ The trial demonstrated a benefit for ACEI therapy (perindopril) only when used in conjunction with a diuretic (indapamide). In the HOPE trial, ramipril demonstrated a significant reduction in the composite endpoint of death, MI, and stroke compared with placebo in a population at high risk of cardiac events.¹⁹ Because a composite outcome was involved, it is not completely clear if ACEI therapy alone reduces the incidence of a second stroke, even though the evidence suggests benefits for ACEI therapy. The latest ACC/AHA guidelines for secondary stroke prevention recommend the use of a thiazide or thiazide combined with an ACEI for secondary stroke prevention.²⁰

Increased risk for cardiovascular events

The use of an ACEI in patients at high risk for cardiovascular events is commonplace and has been investigated in three large clinical trials. The HOPE trial was conducted in a population

with documented coronary artery disease (CAD) or diabetes and additional cardiac risk factors and a normal LVEF.¹⁹ The use of ramipril versus placebo in this study demonstrated a reduction in a composite end point of death, MI, and stroke. The results of HOPE supported the use of ACEI

Trials have not shown ACEIs to be superior to other antihypertensives in the absence of compelling indications (e.g., heart failure, diabetes, myocardial infarction).

in all patients at high risk for cardiovascular events. Similar to HOPE, EUROPA showed that use of perindopril decreased cardiovascular events in high-risk CAD patients.²⁰ The PEACE trial studied high-risk CAD patients treated with trandolapril versus placebo.²¹ The results of PEACE showed no benefit of trandolapril over placebo in reducing cardiovascular events, which conflicts with previous studies. It is thought that the results of the PEACE trial might be attributed to the fact that the majority of patients were medically optimized and a significant percentage of them were revascularized, unlike the patients in

the HOPE study. Thus, in patients at high risk of cardiovascular events, ACEI is recommended. The 2006 AHA/ACC guidelines state that ACEIs should be used in all patients with high cardiovascular risk, but should be considered as optional in patients at low cardiovascular risk.¹⁷

Guidelines strongly recommend therapy with either an ACEI or an angiotensin-receptor blocker (ARB) in diabetic patients to prevent diabetic nephropathy.

Diabetic nephropathy

The literature and a few large studies show a benefit for ACEI use in slowing the progression of diabetic nephropathy. The two largest trials of an ACEI in diabetic nephropathy are the HOPE-MICRO subgroup analysis and the BENEDICT, which both found a benefit based on surrogate markers.^{22,23} In the HOPE-MICRO subgroup study, use of ramipril in diabetic patients reduced the incidence of overt nephropathy (defined as proteinuria). The BENEDICT study demonstrated that trandolapril (versus placebo) reduced the incidence of microalbuminuria in diabetic patients. The 2008 Canadian Diabetes Guidelines and 2010 American Diabetes Guidelines both strongly recommend therapy with either an ACEI or an angiotensin-receptor blocker (ARB) in diabetic patients to prevent diabetic nephropathy.^{24,25}

Conclusions

ACEIs have demonstrated clinical benefits when used in a wide range of cardiovascular disorders. ACEI use reduces mortality after an MI and in heart failure, and are now routinely used in all patients. ACEIs are an option in the treatment of hyperten-

sion, but are no more effective than conventional therapies in uncomplicated cases of hypertension. ACEIs show benefit in secondary stroke prevention, but only when combined with a diuretic. An ACEI should be used in all diabetic patients to reduce the incidence of diabetic nephropathy. ACEI therapy is considered optional in patients at low risk for a cardiovascular event and in patients without compelling indications. ACEIs are considered contraindicated in patients with hyperkalemia, previous angioedema with ACEIs, pregnant patients, and patients with bilateral renal artery stenosis.

Competing interests

None declared.

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