



ACEs and beta-blockers reduce mortality in a broad range of patients

Q: Should everyone with a recent myocardial infarction receive a beta-blocker and an ACE inhibitor?

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A: Yes, except for those with the standard contraindications to these drugs. Otherwise, nearly all patients with a myocardial infarction (MI) should receive a beta-blocker and an angiotensin-converting enzyme (ACE) inhibitor, as no large clinical trial or meta-analysis—and there have been many—has yet demonstrated a subgroup of patients who would not benefit from these drugs in this situation.

Current guidelines from the American College of Cardiology and the American Heart Association (ACC/AHA) suggest that a beta-blocker be started early in an acute MI and continued indefinitely in all patients without contraindications to beta-blockers.¹

Similarly, all patients should receive an ACE inhibitor for at least the first 4 to 6 weeks after an MI. The drug should be continued long-term if the patient has left ventricular systolic dysfunction or heart failure or is felt to be at high risk (eg, due to an anterior or large MI or diabetes), although patients with preserved left ventricular function may receive less benefit than patients with higher risk characteristics.

■ **BENEFIT OF THESE DRUGS**

Large-scale clinical trials consistently show that beta-blockers and ACE inhibitors reduce morbidity and mortality after MI in a broad range of patients. Beta-blockers reduce mortality by 20% to 30% during and after an MI, and ACE inhibitors reduce major cardiac events such as death, recurrent infarction, and heart failure by an additional 15% to 30%.

■ **MECHANISMS OF ACTION**

Beta-blockers prevent catecholamines from binding to beta-1 receptors in the myocardium and peripheral arteries, thus reducing myocardial oxygen demand by decreasing the heart's rate and contractility. They also limit infarct size and recurrent ischemia and reduce automaticity and malignant arrhythmias such as ventricular tachycardia and ventricular fibrillation.

ACE inhibitors improve cardiac hemodynamics by decreasing afterload and preload and dilating the coronary arteries. Their cardioprotective actions may also be related to neurohormonal effects that limit ventricular remodeling and improve endothelial function.

In particular, ACE inhibitors inhibit production of angiotensin II and increase nitric oxide production. The results: decreased vascular and smooth muscle proliferation and migration, diminished oxidative stress, decreased activation of monocytes, macrophages, and platelets, and a reduction in the inflammatory milieu that predisposes to coronary events.²

These neurohormonal effects also play a role in limiting the maladaptive ventricular dilatation and remodeling process that occurs in the weeks and months after an MI.

Arterial inflammation plays a key role in the pathogenesis of coronary artery disease. The addition of ACE inhibitors and beta-blockers to aspirin and a statin may slow this process and help preserve vascular endothelial function.

■ **CONTRAINDICATIONS**

- Contraindications to beta-blockers include:**
- Cardiogenic shock or hypotension



- Bradycardia with a heart rate less than 50
- Any type of second-degree or third-degree atrioventricular block
- Active asthma
- Severe reactive airway disease.

In the past, physicians were reluctant to give beta-blockers to patients with heart failure. Recent trials, however, have shown that beta-blockers reduce mortality in patients with mild, moderate, and even severe heart failure.

Contraindications to ACE inhibitors include:

- Pregnancy
- Hypotension
- Worsening renal insufficiency
- Bilateral renal artery stenosis
- Allergy to an ACE inhibitor.

What about hypotension?

The large-scale trials of beta-blockers and ACE inhibitors all excluded patients with systolic blood pressure lower than 90 to 100 mm Hg at entry. Patients with an initial systolic blood pressure above 100 mm Hg, however, generally tolerate ACE inhibitors and beta-blockers quite well.

In the Fourth International Study of Infarct Survival (ISIS-4), for example, 58,050 patients with MI within 24 hours of enrollment received captopril, isosorbide mononitrate, or placebo.³ In the first 35 days, 5% percent of patients in the captopril group experienced hypotension that required stopping the drug, compared with 2.5% of patients receiving placebo.

Nevertheless, if the blood pressure is on the low side (ie, near 100 mm Hg systolic), it is prudent to give a short-acting ACE inhibitor and a short-acting beta-blocker, cautiously and in small doses (for example, captopril 6.25 mg three times daily and metoprolol 12.5 mg twice daily).

■ START TREATMENT EARLY

The drugs should be started early in the course of MI if the patient is hemodynamically stable. Beta-blockers are generally given intravenously to patients at high risk or with ongoing pain and then changed to an oral regimen.

The Cooperative New Scandinavian

Enalapril Survival Study II trial (CONSENSUS II) showed a trend toward increased mortality in patients who received enalaprilat, an intravenous ACE inhibitor, in the first 24 hours after an infarction,⁴ and as a result only oral ACE inhibitors are used. Nevertheless, rapid titration of ACE inhibitors has been shown to be safe and effective in the first few days after MI, with therapeutic goals in many clinical trials of 50 mg three times per day for captopril, 10 mg twice daily for enalapril, or 10 mg per day for lisinopril or ramipril.

Much of the benefit of beta-blockers and ACE inhibitors is noted in the first 6 weeks after an infarction, and ideally, patients should start these drugs before discharge. If you see an outpatient who was not prescribed a beta-blocker and an ACE inhibitor after a recent MI, these drugs can be started safely on an outpatient basis and gradually titrated to goal doses.

Which is first-line: the beta-blocker or the ACE inhibitor?

A few patients have blood pressure so low they cannot tolerate both a beta-blocker and an ACE inhibitor. In general, beta-blockers are the first-line therapy for ischemic disease, but in these situations it is necessary to carefully evaluate the patient's clinical status, left ventricular function, and comorbidities.

For example, a patient with renal insufficiency and relatively preserved ventricular function would likely benefit most from a beta-blocker. In contrast, in a patient with diabetes, reduced ventricular function, and severe bronchospastic disease, giving an ACE inhibitor alone may be prudent.

Over time, however, most patients with ischemic heart disease tolerate low doses of both a beta-blocker and an ACE inhibitor.

■ RELATIVE CONTRAINDICATIONS

Asthma and mild-to-moderate chronic obstructive pulmonary disease are only relative contraindications to beta-blockers; most patients can tolerate a cardioselective beta-blocker such as metoprolol quite well if it is given in low doses intravenously before starting oral therapy.

Similarly, an abdominal bruit, which can

At discharge only 1/3 of MI patients are receiving these drugs



be a sign of renal artery stenosis, is not an absolute contraindication to an ACE inhibitor, but it does warrant close follow-up of creatinine and potassium levels 3 to 5 days after starting therapy. A rise in creatinine related to an ACE inhibitor generally improves within 1 week of stopping the medication. In the absence of other findings suggestive of renovascular hypertension (eg, severe or refractory hypertension, recurrent episodes of flash pulmonary edema, asymmetric kidney size), we do not routinely screen for renal artery stenosis before starting ACE inhibitors.

■ CAN ARBs BE SUBSTITUTED FOR ACEs?

After starting an ACE inhibitor, 5% to 15% of patients experience a cough and 0.5% develop angioedema related to increased production of bradykinins. Angiotensin II receptor blockers (ARBs) have not been found to cause an increased incidence of cough or angioedema, and in patients who develop these side effects with an ACE inhibitor, substituting an ARB is reasonable.

ARBs and ACE inhibitors appear to have similar antihypertensive effects, but experience with ARBs is limited in patients with heart failure and coronary artery disease. Until more data are available, ACE inhibitors and beta-blockers should remain first-line therapy in patients with coronary disease and heart failure.

■ CONTINUE ACE INHIBITORS IF NO HEART FAILURE?

Some controversy remains about patients with a history of MI but with preserved left ventric-

ular systolic function and no evidence of heart failure.

Evidence from the Heart Outcomes Prevention Evaluation (HOPE) study suggests that all patients with coronary disease may benefit from ACE inhibitors regardless of ejection fraction.⁵ The HOPE study enrolled 9,297 patients with a history of coronary disease, peripheral vascular disease, stroke, or diabetes without left ventricular systolic dysfunction or heart failure and found a 20% reduction in the composite end point of death, MI, or vascular events with ramipril compared with placebo. Nearly 80% of the patients in the HOPE study had a history of coronary artery disease.

On the basis of these results, the ACC/AHA now advocate giving an ACE inhibitor indefinitely to all patients who have had an MI, though they reserve their strongest recommendations for highest-risk patients.⁶

The Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) trial is assessing whether ACE inhibition reduces cardiovascular events in patients with coronary disease and an ejection fraction greater than 40%.⁷ Follow-up is due to be completed in late 2003 and should provide important data on the use of ACE inhibitors in this lower-risk cohort.

■ THERAPY IS UNDERUSED

Even though beta-blockers and ACE inhibitors definitely reduce mortality after an MI, they remain significantly underprescribed. In fact, at hospital discharge, as few as 25% to 30% of MI patients are receiving an ACE inhibitor, and only 30% to 35% are receiving a beta-blocker.

■ REFERENCES

- Braunwald E, Antman E, Beasley J, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: executive summary and recommendations. *Circulation* 2000; 102:1193-1209.
- Dzau V. Mechanism of protective effects of ACE inhibition on coronary artery disease. *Eur Heart J* 1998; 19(suppl J):J2-J6.
- ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: A randomized factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58050 patients with suspected acute myocardial infarction. *Lancet* 1995; 345:669-682.
- Swedberg K, Held P, Kjeksus J, et al. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction. Results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). *N Engl J Med* 1992; 327:678-684.
- 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 (HOPE) Study Investigators. *N Engl J Med* 2000; 342:145-153.
- Smith S, Blair S, Bonow R, et al. AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease: 2001 update. *Circulation* 2001; 104:1577-1579.
- Pfeffer M, Domanski M, Verter J, et al. The Continuation of the Prevention of Events With Angiotensin-Converting Enzyme Inhibition (PEACE) trial. *Am Heart J* 2001; 142:375-377.

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