News and Views from the Literature

Coronary Artery Disease

The PEACE Trial: ACE Inhibitors and Coronary Artery Disease

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Angiotensin-Converting-Enzyme Inhibition in Stable Coronary Artery Disease

Braunwald E, Domanski MJ, Fowler SE, et al; PEACE Trial Investigators.

N Engl J Med. 2004;351:2058-2068.

The Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) trial tested the hypothesis that patients with stable coronary artery disease and normal or slightly reduced left ventricular function would derive therapeutic benefit from the addition of an angiotensin-converting enzyme (ACE) inhibitor—in this case, trandolapril—to modern conventional therapy. The trial was a double-blind, randomized, placebo-controlled study of 8290 patients.

At baseline, the mean age was 64 years, mean blood pressure was 133/78 mm Hg, mean left ventricular ejection fraction was 58 ± 9%. Patients received intensive medical treatment, with 72% having had prior coronary revascularization and 70% having received lipid-lowering drugs. The incidence of the primary endpoint—namely, death from cardiovascular causes, myocardial infarction, or coronary revascularization—was 21.9% in the trandolapril group as compared with 22.5% in the placebo group (hazard ratio in the trandolapril group, 0.96; 95% CI, 0.88-1.06; $P = .43$) over a median follow-up of 4.8 years (Table 1).

The PEACE trial closes a remarkable chapter in the evolution of the role of ACE inhibition in subgroups of patients with myocardial infarction in chronic coronary and cardiovascular disease. The era began in the 1980s with the seminal work of Drs. Marc and Janice Pfeffer using the animal model of experimental myocardial infarction.[1,2] They described the phenomenon of remodeling leading to left ventricular dilatation and failure and further demonstrated that this could be attenuated by ACE inhibition using captopril. The deleterious effects of left ventricular remodeling may result in increased wall stress, increased myocardial infarction demands, subendocardial hypoperfusion, and functional mitral regurgitation. It has been postulated that these events result in the sustained expression of stretch-activated genes such as angiotensin II, endothelin-1, and tissue necrosis factor-α, and that these, in turn, lead to a vicious cycle of further remodeling and heart failure.

These studies were extended into the clinical arena, which in turn led to a series of randomized, controlled trials, the first of which was the Survival and Ventricular Enlargement (SAVE) trial.[3]

Trials in Patients with Acute or Recent Myocardial Infarction

The initial series of trials, namely, SAVE, the Acute Infarction Ramipril Efficacy Study (AIRE), the Survival of Myocardial Infarction Long-Term Evaluation (SMILE), and

Table 1
Incidence of the Primary Endpoint and Its Components and of Death from All Causes in the PEACE Trial

Outcome	Trandolapril N = 4,158 No.	Trandolapril N = 4,158 %	Placebo N = 4,132 No.	Placebo N = 4,132 %	Hazard ratio (95% CI)
Primary (death from CV causes, nonfatal MI, CABG, or PCI)	909	21.9	929	22.5	0.96 (0.88-1.06)
Death from CV causes	146	3.5	152	3.7	0.95 (0.76-1.19)
Nonfatal MI	222	5.3	220	5.3	1.00 (0.83-1.20)
CABG	271	6.5	294	7.1	0.91 (0.77-1.07)
PCI	515	12.4	497	12.0	1.03 (0.91-1.16)
Death from non-CV or unknown causes	153	3.7	182	4.4	0.83 (0.67-1.03)
Death from any cause	299	7.2	334	8.1	0.89 (0.76-1.04)

CV, cardiovascular; MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

the Trandolapril Cardiac Evaluation (TRACE)[4-6] focused on high-risk patients with evidence of extensive left ventricular dysfunction, transient congestive heart failure during myocardial infarction, or anterior myocardial infarctions (because remodeling occurs more frequently in anterior infarcts or in the presence of significant left ventricular dysfunction) (Figure 1).[7] Another study, the Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS) II, in which intravenous enalapril was administered within 24 hours of an acute myocardial infarction, demonstrated a trend toward harm with ACE inhibitors, presumably as a result of hemodynamic instability occurring within the evolving phase of the acute infarction.[8] In contrast, the 4 trials of different ACE inhibitors in high-risk infarct survivors were uniformly positive in regard to the prespecified endpoints of survival, progression of left ventricular dysfunction, and developmental congestive heart failure. The conclusions were clear-cut: the selective use of ACE inhibitors in high-risk patients is strongly indicated, and the duration of administration should be indefinite.

Figure 1. *Impact of ACE inhibitor therapy on mortality. Data from Dries et al.*[7]
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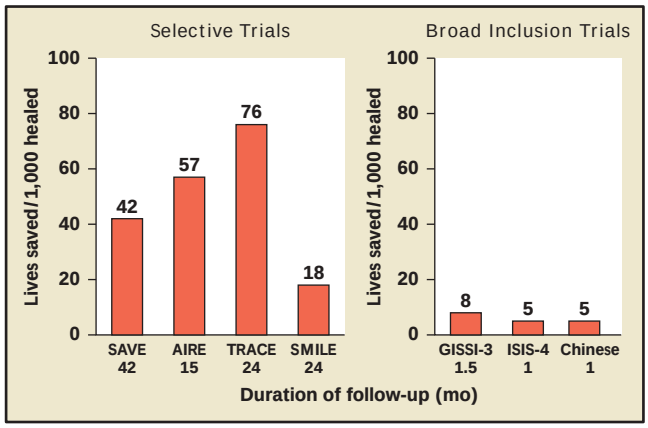


The next phase was characterized by the "inclusive" trials in which ACE inhibitors were administered to virtually all patients with myocardial infarction, but for a shorter period of time (ISIS-4 [Fourth International Study of Infarct Survival], GISSI-3 [Effects of Lisinopril and Transdermal Glycerol Trinitrate Singly and Together on 6-week Mortality and Ventricular Function after AMI], and the Chinese Captopril Trial) (Figure 1).[9-11] These trials were also uniformly positive, but the magnitude of benefit was, as expected, less than that seen among patients at higher risk. This finding led to the recommendation that either approach is acceptable, namely, a *selective* approach using ACE inhibitors indefinitely versus an *inclusive* approach in which all stable patients receive ACE inhibitors followed by reassessment of clinical status in heart failure after a 4- to 6-week period.

Trials in Patients with Chronic Coronary Artery Disease or Cardiovascular Disease

Further analysis of the SAVE trial and from the SOLVD (Studies of Left Ventricular Dysfunction) trials of enalapril and placebo in patients with depressed left ventricular

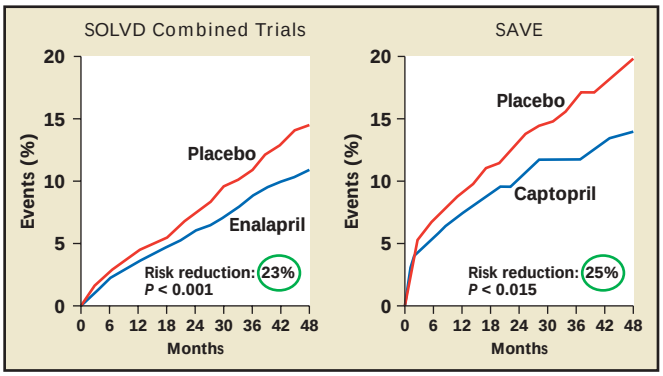
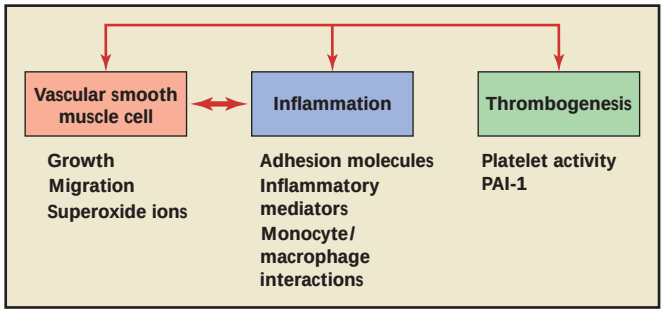


Figure 2. *Cumulative incidence of myocardial infarction in the SOLVD and SAVE trials. Data from Pfeffer MA et al[3] and Yusuf S et al.[12] © 2005 Mayo Clinic Foundation.*

ejection fraction (≤ 36%) and without symptomatic heart failure provided considerable food for further thought (Figure 2).[12,13] It appeared that ACE inhibition was associated with a marked reduction in current ischemic events, and this at first was an unexpected finding. It should be emphasized that the initial rationale for the use of these drugs was to reduce ventricular remodeling and heart failure. Perhaps these unexpected results should have been entirely predictable given the wealth of more recent experimental studies demonstrating that angiotensin II has prothrombotic, proliferative, and proinflammatory properties, all of which could contribute to the progression of atherosclerosis and its instability, namely, plaque rupture (Figure 3). ACE inhibitors, by inhibiting angiotensin II or increasing levels of bradykinin, could attenuate smooth muscle cell contraction and also the generation of reactive oxygen species through stimulation of the NADH/NADPH oxidase systems of the smooth muscle cell. Moreover, bradykinin breakdown is inhibited by ACE inhibitors, and bradykinin-induced augmentation of nitric oxide, at least by the endothelial cell, could be augmented. Angiotensin II inhibition and increased levels of bradykinin also lead to reduced activation of signaling pathways that mediate a number of diverse processes, including vascular inflammation, endothelial dysfunction, activation of matrix metalloproteinases II and IX, atherosclerosis progression, thrombosis, and fibrinolysis.[1]

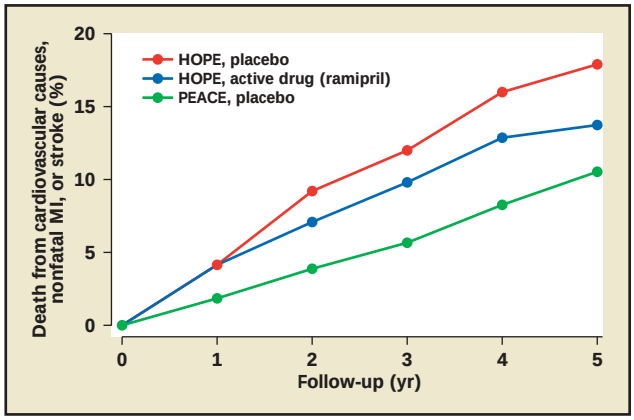
Figure 3. *Links between angiotensin and atherosclerosis. PAI-1, plasminogen activator inhibitor-1. © 2005 Mayo Clinic Foundation.*



These findings led to a series of trials (HOPE [Heart Outcomes Prevention Evaluation], EUROPA [European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease])[14,15] in patients without left ventricular dysfunction but with evidence of coronary artery disease or other vascular disease. In these trials, the objective was to evaluate whether ACE inhibition could reduce subsequent cardiovascular events. HOPE, the first trial to be published, demonstrated a striking benefit from ramipril on a variety of primary and secondary atherosclerotic endpoints in high-risk patients with cardiovascular disease and a *presumed* ejection fraction of 40% or more.

The EUROPA trial using perindopril was also unequivocally positive. The magnitude of the absolute benefit was less than in HOPE, which is to be expected because the EUROPA trial compared a group of patients at much lower risk: they were younger, less likely to be female, and had a much lower frequency of diabetes, peripheral vascular disease, stroke, and prior transient ischemic attacks and hypertension. Moreover, in EUROPA, there was a greater use of aspirin, β-blockers, and lipid-lowering drugs, and total mortality in the placebo group in EUROPA was 7.4% versus 12% in HOPE, with a cardiovascular mortality of 4.4% versus 8.1%. As a result of these two trials, the guidelines were changed. The prior American College of Cardiology/American Heart Association guidelines state, "it is reasonable to consider prescription of ACE inhibitors for all patients with an EF [ejection fraction] of > 0.40 after STEMI [ST-elevation myocardial infarction] as a Class 2a indication,"[16] but the most recent guidelines in 2004 state as a class 1 indication that "an ACE inhibitor should be prescribed at discharge for all patients without contraindications after STEMI."

PEACE, the final trial in this trilogy, did not demonstrate a benefit from ACE inhibitors, and questions have been raised whether these different results are the consequences of a drug-specific as opposed to a class effect. This is highly unlikely given the demonstrable effects of trandolapril on blood pressure lowering in this study and, in a post hoc analysis, its statistically significant beneficial effect on the subsequent development of new-onset diabetes and congestive heart failure as a primary cause of hospitalization or death. Moreover, trandolapril was highly effective in the prior TRACE trial of patients



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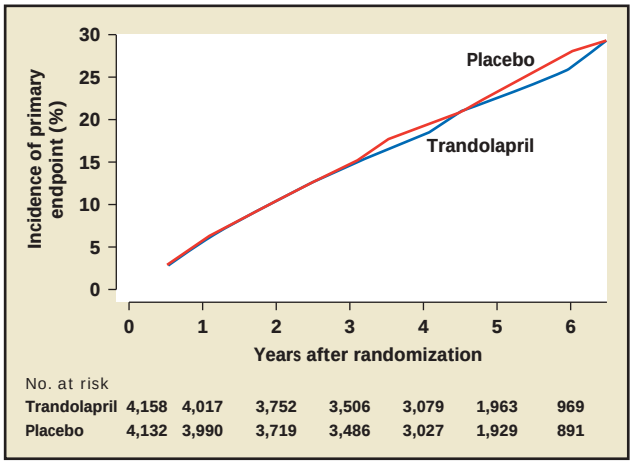

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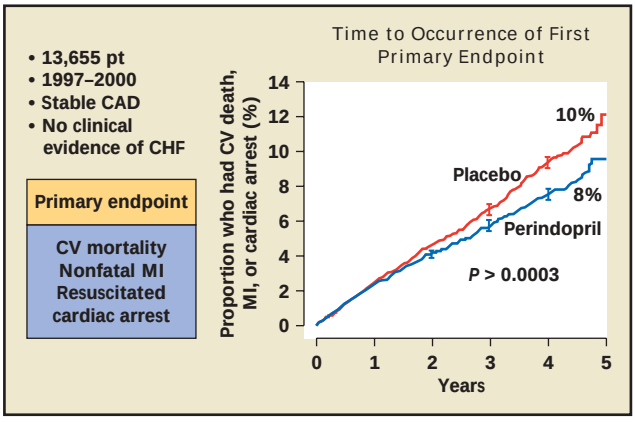

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Figure 4. *The PEACE trial compared with HOPE and EUROPA.* ***(A)*** *Comparison of outcomes in the PEACE and HOPE trials.* ***(B)*** *Cumulative incidence of the primary endpoint, according to treatment group, in the PEACE trial.* ***(C)*** *The EUROPA trial: perindopril in stable coronary artery disease (CAD). CHF, congestive heart failure; CV, cardiovascular; MI, myocardial infarction. Data in part C from Fox KM and the EUROPA Investigators.*[15] *© 2005 Mayo Clinic Foundation.*

with left ventricular dysfunction, at the 4 mg/d dosage adopted by PEACE.

To place this trial in the context of HOPE and EUROPA, it is useful to compare both the baseline characteristics and the rates of events. At baseline, the resting blood pressure in PEACE (133/78 mm Hg) was similar to that achieved on an ACE inhibitor in both HOPE and EUROPA. The average ejection fraction in PEACE was 58%, and average creatinine and cholesterol levels were normal. At baseline, PEACE patients had received more intensive management, including a higher dose of lipid-lowering agents and a 72% rate of prior revascularization. Thus, it is not surprising that the subsequent rate of cardiovascular events in the placebo arm of PEACE was low. Indeed, placebo-treated patients in PEACE had a substantially lower event rate than did ramipril-treated patients in HOPE (Figure 4). Moreover, the proportions of death due to cardiovascular causes were 63% in HOPE, 59% in EUROPA, 47% in PEACE, and 35% in an age- and sex-matched general population.

In an editorial accompanying the article by Braunwald and colleagues, Dr. Pitt refers to two trials with quinapril that provide further support for the hypothesis that the negative results in the PEACE trial were related to the level of baseline risk. In the Trial on Reversing Endothelial Dysfunction (TREND), in which the ACE inhibitor quinapril was shown to be effective in improving endothelial function in patients with coronary disease but without left ventricular systolic dysfunction, a retrospective analysis of the data demonstrated that the drug was effective only among patients whose low-density lipoprotein (LDL) cholesterol was above 125 mg/dL.[17]

The most plausible explanation for the lack of benefit from ACE inhibitors in PEACE is that the patients who were enrolled were at a lower risk for cardiovascular events.

Further support is provided by the Quinapril Ischemic Event Trial (QUIET), in which quinapril overall failed to reduce the rate of cardiovascular events but did appear to be effective in reducing the rate of progression of coronary artery disease and cardiovascular events among patients with increased concentrations of serum LDL cholesterol.[18]

In summary, the most plausible explanation for the lack of benefit from ACE inhibitors in PEACE is that the patients who were enrolled were at a lower risk for cardiovascular events. It would appear that ACE inhibitors are not always necessary in patients with coronary artery disease in order to reduce cardiovascular deaths, particularly among patients intensively treated with risk factor modification and prior revascularization. This is an important conclusion given that many elderly patients are unable to tolerate multiple drugs, particularly those with borderline hypotension. Nonetheless, this trial does not negate the role of ACE inhibitors in patients with diabetes, hypertension, or left ventricular dysfunction and/or severe vascular disease. Moreover, even in a low-risk population, it is not easy to distinguish individual patients from those enrolled in EUROPA as opposed to those in PEACE, and in such patients, physicians may still wish to consider ACE inhibition. What should be emphasized, however, is that ACE inhibitors should be considered in such patients but are not mandatory.

Use of Angiotensin I Receptor Blockers

Considerable interest has been directed toward the objective of more complete angiotensin II blockade by the use of the angiotensin I receptor blockers. It is not the purpose of this review to discuss all such trials, but in myocardial infarction patients, VALIANT (Valsartan in Acute Myocardial Infarction Trial) compared the role of valsartan, captopril, or both in 14,708 high-risk patients with myocardial infarction within the previous 10 days.[19] Patients had left ventricular systolic dysfunction, congestive heart failure, or both. The conclusions were quite clear-cut with regard to mortality from any cause or the combined endpoint of cardiovascular death, reinfarction, or hospitalization for heart failure. There was equivalence between valsartan and captopril and no benefit from the combination. The initial drug of choice, therefore, should be an ACE inhibitor given that it is cheaper, but valsartan is certainly an effective alternative for patients with ACE inhibitor intolerance. The ongoing ON TARGET (Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) and TRANSCEND (Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease) trials are comparing telmisartan, ramipril, and their combination in high-risk patients with previous vascular events or diabetes with target-organ damage but a controlled blood pressure and no heart failure. The ON TARGET trial will enroll 23,400 patients and TRANSCEND, 6000 patients.[20] These studies will provide data regarding the role of angiotensin receptor blockers in patients with vascular disease.

In summary, we have seen almost 2 decades of trials that have established the role of blockade of the renin-angiotensin system in patients with congestive heart failure, myocardial infarction, or stable coronary artery disease.[21] The PEACE trial makes a further contribution to this field by suggesting that there is a "floor," as defined by a low level of baseline risk, at which the addition of ACE inhibitors may not result in an increase in benefit. It should be emphasized, however, that this floor is reached only by achieving excellent blood pressure control and using β-blockers, lipid-lowering therapy, aspirin, and, in many patients, prior coronary revascularization. ■

References

1. Pitt B. ACE inhibitors for patients with vascular disease without left ventricular dysfunction—may they rest in PEACE [editorial]? *N Engl J Med*. 2004; 351:2115-2117.
2. Pfeffer MA, Pfeffer JM, Steinberg C, Finn P. Survival after an experimental myocardial infarction: beneficial effects of long-term therapy with captopril. *Circulation*. 1985;72:406-412.
3. 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.
4. Ambrosioni E, Borghi C, Magnani B. The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. The Survival of Myocardial Infarction Long-Term Evaluation (SMILE) Study Investigators. *N Engl J Med*. 1995; 332:80-85.
5. Kober L, Torp-Pedersen C, 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.
6. 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.
7. Dries DL, Solomon AJ, Gersh BJ. Adjunctive therapy after reperfusion therapy in acute myocardial infarction. *Clin Cardiol*. 1998;21:379-386.
8. Swedberg K, Held P, Kjekshus 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.
9. Chinese Captopril Study Investigators. Oral captopril versus placebo among 13,634 patients with suspected acute myocardial infarction. *Lancet*. 1995;345:686-687.
10. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulfate in 58,050 patients with suspected acute myocardial infarction. *Lancet*. 1995;345:669-682.
11. The GISSI-3 Study Group. GISSI-3: effects of lisinopril and transdermal glycerol trinitrate singly and together on 6 week mortality and ventricular function after acute myocardial infarction. *Lancet*. 1994;343:1115-1122.
12. Yusuf S, Pepine CJ, Garces C, et al. Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. *Lancet*. 1992;340:1173-1178.

13. 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.
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 [errata appear in *N Engl J Med*. 2000;342:748 and 2000;342:1376]. *N Engl J Med*. 2000;342:145-153.
15. Fox KM; EUROPA Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (The EUROPA study). *Lancet*. 2003;362:782-788.
16. Smith SC Jr, Blair SN, Bonow RO, et al. AHA/ACC scientific statement: AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease: 2001 update: a statement for health-care professionals from the American Heart Association and the American College of Cardiology. *Circulation*. 2001;104:1577-1579.
17. Mancinni GB, Henry GC, Macaya C, et al. Angiotensin-converting-enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary artery disease [erratum appears in *Circulation*. 1996;94:1490]. *Circulation*. 1996;94:258-265.
18. Pitt B, O'Neil 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.
19. Pfeffer MA, McMurray JJ, Valazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med*. 2003;349:1893-1906.
20. The ONTARGET/Transcend Investigators. Rationale, design, and baseline characteristics of 2 large, simple, randomized trials evaluating telmisartan, ramipril, and their combination in high-risk patients: the ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND) trials. *Am Heart J*. 2004;148:52-61.
21. Latini R, Maggioni AP, Flather M, et al. ACE inhibitor use in patients with myocardial infarction. Summary of evidence from clinical trials. *Circulation*. 1995;92:3132-3137.

Acute Coronary Syndromes

Novel Serum Markers for Risk Prediction in Acute Coronary Syndromes

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One of the most difficult problems in medicine is evaluating the patient who presents with chest pain. Among the myriad causes of chest pain are benign conditions such as costochondritis, serious but not life-threatening conditions such as pericarditis, and the truly life-threatening situations, such as acute coronary syndromes. Differentiating among these pathologies is sometimes quite difficult; thus new methods to separate the benign from the life threatening are being sought. It is increasingly recognized that atherosclerosis is an inflammatory disease.[1] Chronic, subclinical inflammation appears to be one mechanism leading to atherosclerotic plaque rupture and acute coronary syndromes. If, indeed, inflammation underlies acute coronary syndromes, then inflammatory molecules should be elevated in patients in the midst of acute coronary syndromes. Two recent papers address this phenomenon and are reviewed below.

Prognostic Value of Myeloperoxidase in Patients with Chest Pain

Brennan ML, Penn MS, Van Lente F, et al.
N Engl J Med. 2003;349:1595-1604.

Myeloperoxidase is an enzyme released by inflammatory cells and found to be present in atherosclerotic plaques. In this study, the predictive value of myeloperoxidase was assessed in 604 consecutive patients presenting to an emergency department with 24 hours or less of chest pain. All patients had a single baseline myeloperoxidase level drawn, then were followed up for 6 months for the combined endpoint of myocardial infarction (MI), coronary revascularization, or death.

Findings

Patients were stratified into quartiles by their baseline level of myeloperoxidase, and it was found that the incidence of myocardial infarction increased with increasing quartiles of myeloperoxidase; 13.9% of patients in quartile 1 had MI, 16.6% of patients in quartile 2, 25.2% in quartile 3, and 38.4% in quartile 4 ($P < .001$ for trend). Baseline myeloperoxidase levels also predicted the risk of major adverse cardiac events over the following 30-day and 6-month periods. The investigators also found that plasma myeloperoxidase levels predicted cardiovascular risks independently of the levels of C-reactive protein and other markers of inflammation.

Patients were stratified into quartiles by their baseline level of myeloperoxidase, and it was found that the incidence of myocardial infarction increased with increasing quartiles of myeloperoxidase.