Diabetes mellitus affects ~6% of the US population but is present in as many as 30% of patients hospitalized with acute coronary syndromes. It has been recognized for some time that diabetics experience a greater mortality during the acute phase of myocardial infarction (MI) and a higher morbidity in the postinfarction period (see recent reviews in References 1 and 2). Before the advent of coronary care as we know it today, mortality among diabetic patients in MI was reported to be as high as 40% and at least double the mortality rate in patients without diabetes. More extensive coronary artery disease, additional cardiovascular risk factors, and other end-organ disease were thought to be largely responsible for this major difference in outcome. Current treatment of acute MI derived from large clinical trials has dramatically improved survival in both nondiabetic and diabetic patients. However, despite these improvements, diabetes still doubles the case-fatality rate. In the GUSTO-1 angiography substudy report, this twofold increase in relative risk of 30-day mortality persisted even after adjustment for the factors cited above. What is this “diabetic factor”? It is in this context that new information on this topic must be evaluated.

In the December 16, 1997, issue of Circulation, the GISSI-3 investigators compare the effect of early administration (within 24 hours of admission) of lisinopril in patients with and without diabetes mellitus in MI. Compared with placebo, lisinopril dramatically reduced both 6-week and 6-month mortality in diabetics versus nondiabetics (6 weeks, 30% versus 5% and 6 months, 20% and 0%, respectively). Furthermore, the incidence of drug-related adverse effects was similar between the two groups within the blood pressure and renal function parameters used in that study. This experience, along with the subgroup analyses of SAVE and TRACE, should firmly establish an ACE inhibitor as part of the regimen for the diabetic patient with MI. In a recent meta-analysis of ACE inhibitor trials in acute MI, only a 6% relative mortality reduction (without regard to the presence or absence of diabetes mellitus) was found with early drug administration. Despite these collective data, ACE inhibitors are generally withheld on the first day of acute MI to avoid causing hypotension. In CONSENSUS II, hypotension in the enalapril-treated group negated any potential benefit of early ACE inhibition. This GISSI-3 report also suggests that the diabetic patient may have far more to gain than the nondiabetic when an ACE inhibitor is administered within the first day of an acute MI. The putative mechanisms responsible for the major benefit of ACE inhibition in these patients are presented below.

In general, ACE inhibitors are grossly underprescribed in this setting, despite their recognized benefits. The failure to use them in diabetic patients may be even more prevalent, for the following reasons: (1) fear of azotemia with or without preexistent renal disease; (2) fear that they may cause or contribute to hemodynamic instability, particularly if diabetes-related autonomic neuropathy is suspected; (3) fear that they may induce hyperkalemia, because type 4 RTA or bilateral renal artery stenoses are more common in diabetics; and (4) preoccupation with the challenge of glycemic control. A similar paradox relates to the failure to administer β-blockers to diabetic patients in acute MI. Compared with placebo in this setting, β-blockers provide two to three times the relative benefit in mortality reduction when diabetes is present compared with when it is absent. However, the risk of masking the warning signs of hypoglycemia and disturbing glycemic control tends to limit their use. Although these are valid concerns, insulin-induced hypoglycemia occurs far less commonly in type II than in type I diabetic patients, and cardioselective β-blockers can be given in doses providing secondary prevention with less effect on glucose metabolism than nonselective agents. Much of the reluctance to administer these agents stems from warnings issued years ago when only nonselective β-blockers were available and were typically prescribed in much higher dosages.

The GISSI-3 authors address only briefly the potential mechanisms underlying the benefit of lisinopril in diabetic patients. Both inhospital and late mortality after acute MI are highly correlated with the degree of left ventricular dysfunction. A major determinant of this prognostic variable is left ventricular remodeling, a process involving expansion of the infarcted segment with subsequent ventricular dilatation and asynergy of the noninfarcted regions. After adjustment for the size of infarction, diabetic patients experience more congestive heart failure than nondiabetic patients, which suggests that the behavior of the noninfarct zone may be an important determinant in the outcome between the two groups. For many years, more extensive coronary artery disease in the diabetic patient was thought to explain the greater degree of left ventricular dysfunction. In GUSTO-1, however, the twofold increase in relative risk of 30-day mortality conferred by the presence of diabetes remained unaltered after adjustment for extent of coronary artery disease and a variety of other clinical factors.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Cardiovascular Division, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Mass (R.W.N.) and the Cardiovascular Division, Bridgeport Hospital, Yale University Medical School, Bridgeport, Conn (S.Z.).

Correspondence to Richard W. Nesto, MD, 110 Francis St, Suite 4B, Boston, MA 02215.
E-mail nesto@west.bidmc.harvard.edu

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Richard W. Nesto, MD; Stuart Zarich, MD
Many conditions specific to the heart in diabetes affect global myocardial remodeling. Previous silent infarction may be present in as many as 40% of these patients at the time they present with their first clinically recognized MI. Cardiac autonomic neuropathy may be present in nearly 50% of the diabetic population with coronary artery disease and can cause both diastolic and systolic dysfunction. Cardiomyopathy secondary to diabetes is often subclinical, with diastolic dysfunction typically preceding systolic dysfunction. Hypertension and diabetes together result in more cardiac fibrosis than when either occurs alone. Endothelial dysfunction may impair coronary perfusion at the microvascular level, resulting in ischemia. Although the heart utilizes free fatty acids as its major source of energy, ischemia results in greater expression of GLUT4 transporter proteins, facilitating glucose entry and glycolysis, a major source of myocardial ATP in anaerobic conditions. In diabetes, however, ATP generation is less efficient, because relative insulinopenia results in increased lipolysis, elevated plasma levels of free fatty acids, and increased fatty acid oxidation as glycolysis and glucose oxidation are suppressed. In addition, despite the hyperglycemia most diabetics experience in acute MI, glucose is unavailable as an energy source, because myocardial GLUT4 transporter protein levels may be depressed. These metabolic perturbations result in depressed ATP production, generation of oxygen free radicals, increased myocardial oxygen consumption, and myocardial contractile dysfunction. It is not surprising that additional myocardial damage results in heart failure out of proportion to infarct size in patients with diabetes.

Several studies support the notion that the structural, functional, and metabolic factors related to diabetes cited above place the left ventricle at higher risk for maladaptive remodeling. One study comparing serial wall motion scores after MI showed that left ventricular function at discharge and at 6 months remained stable in nondiabetic patients, whereas it progressively deteriorated in the patients with diabetes. Iwasaka and coworkers, using radionuclide angiography, found that regional ejection fraction of the noninfarct zone at any end-diastolic volume 3 weeks after MI was lower in patients with diabetes, despite infarct size and extent of coronary artery disease similar to those in the group without diabetes. Diabetic patients demonstrated more global and regional left ventricular dysfunction 4 weeks after inferior MI than their nondiabetic counterparts in another study that used radionuclide ventriculography.

Remodeling of the left ventricle consequent to MI is a time-dependent phenomenon. Increases in end-diastolic and end-systolic volumes may be seen within 3 hours of admission and serve as strong predictors of both early and late outcome. In the HEART study, early ramipril administration in anterior infarction was associated with substantial recovery of wall motion by 14 days, prompting the investigators to say that “the major mortality and echocardiographic studies would support early initiation of ACE inhibition in acute MI, especially in higher-risk individuals in whom this therapy should be maintained on a long-term basis.” In the parent GISSI-3 report, nearly one half of the lives saved with early lisinopril use were a result of a reduction in deaths secondary to cardiac rupture and pump failure. Indeed, diabetes is a risk factor for rupture of the ventricular free wall complicating infarction.

In addition to beneficial effects on ventricular remodeling, ACE inhibitors can further improve outcomes by reducing recurrent ischemic events (MI, unstable angina, and revascularization) after MI. ACE inhibition reduced recurrent MI by 25% in the SAVE trial and was associated with 37% fewer ischemic events after infarction in the CATS trial. Salutary effects on neurohumoral activation, oxidative stress, endothelial function, ischemic preconditioning, and fibrinolysis provide further insight into the preferential effect of ACE inhibition in diabetic subjects in the postinfarction period.

Epidemiologic studies suggest that enhanced sympathetic activity is associated with an increased risk for ischemic events and sudden death. Sympathetic activation increases both the hemodynamic and hemostatic risk factors, leading to plaque rupture and thrombosis. A substantial number of type I and type II diabetic patients (with or without clinical signs of autonomic nervous system dysfunction) have diminished vagal activity, resulting in relatively higher sympathetic activity (sympathovagal imbalance) during the day and night. Diabetics with autonomic neuropathy are at increased risk of cardiac events and show an altered circadian pattern of ischemia compared with diabetics without autonomic dysfunction. In general, sympathovagal imbalance documented by heart rate variability studies has been associated with a poor prognosis after MI independent of left ventricular dysfunction.

In GISSI-3, the diabetic subgroup presented with a higher Killip classification and higher heart rate, suggesting more pronounced activation of both the adrenergic and renin-angiotensin systems than in their nondiabetic counterparts. In general, ACE inhibition is most effective in patients with the greatest degree of neurohumoral activation, which helps to explain the magnitude of benefit of ACE inhibitors in diabetics after infarction in this study. ACE inhibitors increase parasympathetic tone and restore autonomic balance in congestive heart failure. There is increasing evidence that ACE inhibition may attenuate sympathetic responses. ACE inhibitors may decrease central sympathetic outflow, alter post sympathetic α-adrenergic tone, and blunt sympathetic coronary vasoconstriction by decreasing angiotensin II production. Altered sympathetic tone may also be responsible for the potential of ACE inhibitors to reduce ventricular arrhythmias. Although ACE inhibitors may be able to modify sympathovagal balance, diminishing angiotensin II levels, little is known regarding their effects on patients with diabetes-related autonomic neuropathy.

Increased oxidative stress brought about by hyperglycemia may be an important link between diabetes and vascular events. Advanced glycosylated end products may quench nitric oxide through the generation of oxygen free radicals, leading to impaired endothelial vasodilatation. Angiotensin II augments oxidative stress by increasing the vascular production of superoxide radicals, which in turn interfere with the bioavailability of nitric oxide. By increasing free radical production, angiotensin II increases leukocyte adhesion to the endothelium, platelet aggregation, and cytokine expression, resulting in macrophage infiltration at the site of atherosclerotic plaques, leading to increased plaque vulnerability. ACE accumulation has recently been demonstrated within inflammatory regions of atherosclerotic plaque. ACE inhibitors improve endothelial function in atherosclerotic vessels.
Diabetes alone or in combination with a variety of risk factors (hypertension, hypercholesterolemia) can impair endothelial function. ACE inhibitors have recently been found to normalize endothelial function in type I diabetics via a nitric oxide–mediated mechanism in the short term, with further improvements in vasodilatation after 4 weeks of treatment. 

Because bradykinin antagonists have been shown to reverse the salutary changes of ACE inhibition on endothelium–dependent vasodilatation, accumulation of endogenous bradykinin, which directly stimulates nitric oxide production, plays a major role in the vascular effects of ACE inhibition. 

Angiotensin II can also alter vasomotor tone directly or indirectly by increasing endothelin generation. Because bradykinin antagonists have been shown to reverse the salutary changes of ACE inhibition on endothelium–dependent vasodilatation, accumulation of endogenous bradykinin, which directly stimulates nitric oxide production, plays a major role in the vascular effects of ACE inhibition. 

In diabetic patients, ACE inhibitors may be particularly beneficial by improving endothelial function and vascular tone and augmenting ischemic preconditioning.

Impaired fibrinolysis, as reflected by elevated plasminogen activator inhibitor (PAI)–1 levels, has been associated with an increased risk of recurrent MI. Plasma PAI–1 is increased in diabetic patients and has been linked to vascular disease. The recent ECAT study documented the association of impaired fibrinolysis, parameters of endothelial cell dysfunction, and an inflammatory state with future adverse coronary events. 

PAI–1 activity and antigen predicted that cardiac events were related principally to insulin resistance. ACE inhibitors can suppress plasminogen activator expression experimentally and improve fibrinolytic capacity in patients after MI. ACE inhibitors also markedly improve insulin sensitivity and glycemic control. Acute hyperglycemia can in itself increase vascular tone, presumably by decreasing nitric oxide availability. Because improved glycemic control is associated with improved mortality after MI in diabetic patients receiving insulin, ACE inhibitors may improve survival in this group by decreasing insulin resistance, improving glycemic control, and restoring fibrinolytic capacity.

ACE inhibitors counteract many of the established and putative mechanisms accounting for the increased mortality of MI in diabetes mellitus. Is the greater relative mortality reduction in diabetes simply explained by the fact that these agents defend against mechanisms shared by both groups, or are there mechanisms specific to diabetes against which ACE inhibitors might be operative? The authors of this study broach this question by showing that diabetic patients benefited more from lisinopril than nondiabetic patients, independent of other risk factors for elevated mortality. The prevention or retardation of nephropathy in the diabetic patient is a good example in which ACE inhibitors act by diabetes–specific (lowering efferent arteriolar tone) and –nonspecific (lowering systemic blood pressure) mechanisms. Further elucidation of the role of the renin-angiotensin system in acute coronary syndromes in diabetic patients will answer this question.

It appears that the entire benefit of early administration of lisinopril in GISSI 3, as reported initially, could be explained by the marked effect in patients with diabetes, who composed only 6.5% of the total study population. In a post hoc analysis conducted in ISIS 2, the presence of diabetes was the only clinical factor that altered the interaction of aspirin and streptokinase on mortality in acute MI. Although the results of these subgroup analyses are interesting, the implications for practice are somewhat limited by their post hoc nature. The rewards of specifying a subgroup for analysis are exemplified in the recent BARI trial, which showed that in the presence of diabetes, coronary bypass surgery provided a survival benefit over PTCA in multivessel disease, even though no difference between treatments was noted for the entire study population. Because diabetes mellitus profoundly affects the biology of cardiovascular disease, one could argue that clinical trials in the future with potential major implications for the care of patients with heart disease should be specifically designed to evaluate the effect of therapy in patients with diabetes mellitus.

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