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Emerging Concepts in the Management of Acute Myocardial Infarction in Patients With Diabetes Mellitus

Koon-Hou Mak, MBBS,* Eric J. Topol, MD†
Singapore and Cleveland, Ohio

Although fibrinolysis has improved survival of patients after myocardial infarction (MI), such therapy is less likely to be administered to patients with diabetes. Furthermore, these patients present later (15 min) than nondiabetics. Moreover, even with the use of early potent fibrinolytic agents, patients with diabetes continued to suffer excessive morbidity and mortality. This finding is not related to the ability of fibrinolytic agents to restore complete reperfusion or increased risk of reocclusion of the infarct-related artery. Instead, the impaired ventricular performance at the noninfarct areas and metabolic derangements during the acute phase of MI may account for the adverse outcome. The efficacy of percutaneous coronary revascularization procedures for treatment of acute MI requires further evaluation. Therapeutic approaches should consider correcting these abnormalities to afford greater survival benefit for this subset of high-risk patients. (J Am Coll Cardiol 2000;35:563–8) © 2000 by the American College of Cardiology

The Framingham study has clearly demonstrated that cardiovascular mortality was heightened among patients with diabetes. This trend is particularly evident following acute myocardial infarction (AMI) (1). Although the use of fibrinolytic therapy in the treatment of AMI has resulted in a considerable improvement of survival, diabetes remained an important independent predictor for mortality (2). This review will examine the issues that may account for this unfavorable prognosis and promising avenues to further improve outcomes.

OVERVIEW OF FIBRINOLYSIS

In a major international trial involving more than 40,000 patients designed to evaluate four fibrinolytic strategies for the treatment of AMI, 30-day mortality was 6.2% among patients without diabetes and 10.5% among patients with diabetes (Fig. 1). Indeed, by pooling the data from several large fibrinolytic trials with a total of more than 80,000 patients, the one-month mortality was increased by 1.7 times among diabetics. Notably, mortality was highest among those treated with insulin. Mortality for patients treated with insulin was at least 1.3 times greater than for noninsulin diabetics. In fact, the difference in mortality between patients with and without diabetes continues to increase after 30 days. By the end of the first year, the relative risk for mortality for patients with diabetes has risen from ~1.4 to ~1.6 times (3).

Impaired delivery of care. Fibrinolytic therapy has undoubtedly improved outcome of patients after AMI (4,5). Perhaps less known is the fact that fibrinolysis saved 37 lives per 1,000 patients with diabetes at 35 days, compared with 15 per 1,000 patients without diabetes (6). Thus, the absolute benefit is more than doubled for fibrinolytic therapy among diabetics. Despite its tremendous benefit, diabetics were less likely to receive fibrinolytic therapy (7), as evident in the Survival and Ventricular Enlargement (SAVE) Study. This trial was designed to evaluate the efficacy of captopril in reducing mortality and morbidity in survivors of AMI with baseline left ventricular dysfunction. Use of fibrinolytic therapy was left to the discretion of the attending physician. Of 2,231 patients enrolled, fibrinolytic therapy was administered in 733 (32.9%). Among various epidemiological parameters studied, the presence of diabetes emerged as an independent variable for not using fibrinolytic therapy (Fig. 2). Importantly, these findings extend beyond the context of a clinical trial. In a recent report from a large national AMI registry (8), 272,651 patients with an AMI enrolled from almost 1,500 hospitals during the period of June 1994 to July 1996. Of these, 84,663 (31%) were considered to be eligible for reperfusion therapy. Although the proportion of patients (76%) who actually received this mode of treatment was greater than the SAVE study (7), the factors associated with failure to use reperfusion therapy were quite similar. Indeed, using univariate analysis, the odds for patients with diabetes mellitus to

From the *Department of Cardiology, Tan Tock Seng Hospital, Singapore; and the †Department of Cardiology, Joseph J. Jacobs for Thrombosis and Vascular Biology, The Cleveland Clinic Foundation, Cleveland, Ohio.

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Abbreviations and Acronyms

AMI	=	acute myocardial infarction
ATP	=	adenosine triphosphate
CI	=	confidence interval
FFA	=	free fatty acids
GIK	=	glucose-insulin-potassium
GUSTO-I	=	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries
MI	=	myocardial infarction
PTCA	=	percutaneous transluminal coronary angioplasty
SAVE	=	Survival and Ventricular Enlargement Study
TIMI	=	Thrombolysis in Myocardial Infarction

receive reperfusion therapy was almost half compared with nondiabetics. The presence of diabetes mellitus remained as an independent predictor for a lower likelihood for reperfusion therapy in a multivariate statistical model (OR 0.67; 95% confidence interval [CI], 0.52 to 0.87). This unfavorable trend was also observed in a nationwide French survey (37% vs. 46%, for diabetic and nondiabetic patients receiving reperfusion therapy, respectively; $p = 0.001$) (9) and the United Kingdom (37% vs. 54%, for diabetic and nondiabetic patients receiving reperfusion therapy, respectively; $p < 0.05$) (10). However, as with several of these clinical studies, the reasons for this finding are largely unknown and probably attributed to numerous factors, such as atypical or late presentation and undue concern regarding the adverse effects of fibrinolysis. In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) study (3), there was only a marginal increase in moderate bleeding complications (13% vs. 11%) without an increased risk in major bleeding rates. More importantly, the risk of intracranial hemorrhage was similar between patients with and without diabetes (0.6% vs. 0.7%; $p > 0.05$). Furthermore, intraocular hemorrhage did not occur in any of the 6,011 diabetic patients although there was one patient with periorbital hematoma from a fall. So the upper 95% CI for intraocular hemorrhage in patients with diabetes was 0.05% (11). Hence, administration of fibrinolytic agents is not associated with increased complications. When there are no usual contraindications, physicians should be encouraged to treat diabetic patient with fibrinolytic agents for AMI (12).

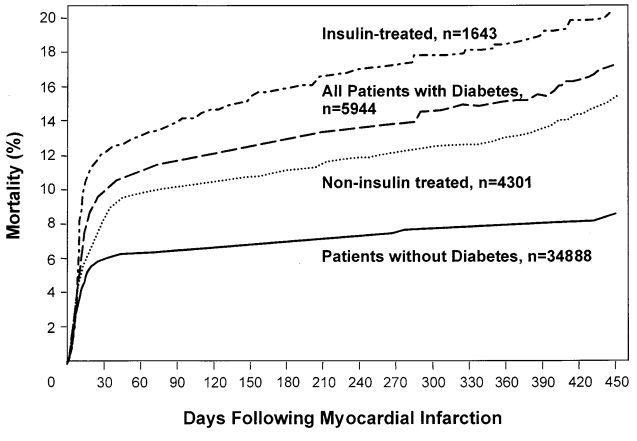

Figure 1. Kaplan-Meier estimates of cumulative mortality by diabetes status in the GUSTO-I Study (3).

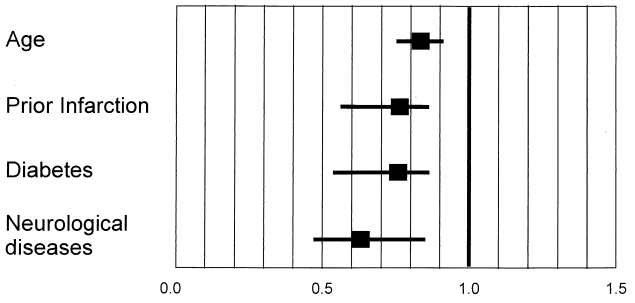

Figure 2. Odds ratio in a multiple logistic regression model for predicting the use of fibrinolysis in the SAVE Trial. SAVE = Survival and Ventricular Enlargement Study.

Another major drawback for diabetic patients was that they were receiving fibrinolytic therapy (15 min later [3]). Although the reason for this delay is unclear, the impaired sensation of pain may be contributory (13). From the pooled data of almost 69,000 patients, the Fibrinolytic Therapy Trialists' Group (6) found that mortality was 1% higher for every hour lag in treatment. As such, a rational approach in improving outcome of diabetic patients with AMI is to educate these patients on the importance of early presentation and atypical manifestations of AMI (14). Furthermore, oral hypoglycemic agents are known to cause repolarization abnormalities on the resting electrocardiogram. In particular, some animal studies suggest (15,16) that the amplitudes of ST-segment elevation and T-wave peaking may be reduced with these medications and, therefore, lowered the sensitivity of the electrocardiogram in identifying such patients with AMI. Physicians are to maintain a high index of suspicion to recognize these patients. However, the success of this strategy does not depend only on the sincere efforts of healthcare providers and extensive public education programs. To further improve outcomes of this subset of high-risk patients, other barriers of health care delivery, such as financial and logistical, must be overcome by an effective national health policy (17).

Possible impaired fibrinolysis. In addition to bias against the use of fibrinolytic agents and later presentation, patients with diabetes have enhanced platelet activity, elevated procoagulant levels and impaired intrinsic fibrinolysis (18). These abnormalities are believed to account for, at least in part, the deleterious clinical course of diabetic patients with AMI as the efficacy of fibrinolytic agents may be reduced. The importance of a prompt response to fibrinolysis in

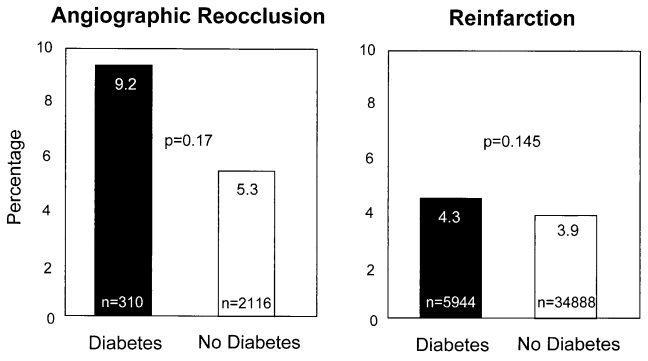

Figure 3. In-hospital angiographic reocclusion and 30-day reinfarction rates after fibrinolysis in the GUSTO-I Study.

achieving early and complete reperfusion of the infarct-related artery is clearly demonstrated by the data from a large angiographic study of patients with AMI (19). Patients with Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow showed a substantial reduction in 30-day mortality compared with those with TIMI flow grades 0 or 1, with an odds ratio of 0.46 (95% CI, 0.25–0.86). By pooling the results of 4,687 patients undergoing coronary angiography after myocardial infarction (MI), mortality was lowest among those with TIMI grade 3 flow (3.7%), intermediate among those with TIMI grade 2 flow (6.6%) and greatest among those with TIMI grade 0 or 1 flow (9.2%) at 90 min (20).

However, there was little difference in the TIMI flow grades between patients with and without diabetes (21). This finding was, in some ways, unexpected, and, therefore, the excess mortality associated with patients with diabetes cannot be attributed to reduced patency response to fibrinolytic therapy. However, TIMI flow may not accurately reflect myocardial flow among patients with diabetes. Underlying endothelial dysfunction (22,23) and diminished myocardial flow reserve (24) may contribute to poorer outcomes despite similar TIMI flow grades.

In addition to the similar TIMI flow grades, there were no differences in the rates of angiographic reocclusion (21) and reinfarction (3) between patients with and without diabetes (Fig. 3). Nonetheless, it must be recognized that in the angiographic study, the proportion of patients who died before follow-up angiography was almost three-fold higher for diabetic patients (21). Since these patients were more likely to suffer from reocclusion, the question as to whether angiographic reocclusion rates were between patients with and without diabetes remains to be answered conclusively. Likewise, in the clinical trial, patients with diabetes may be more inclined to suffer from silent reinfarction and may have avoided detection. But the contribution of this premise to account for the unfavorable outcomes of diabetic patients is uncertain. These potential limitations underscore the problems associated with retrospective subgroup analysis and the importance of a prospective study to confirm these observations.

In contrast, recurrent ischemia occurred more commonly among diabetics (22% vs. 20%, $p < 0.001$) (3). The inability to maintain vessel patency is known to result in drastic consequences, including higher complication, revascularization and mortality rates (25,26). This problem may be related to the poorer outcome of patients with patients. As the increased rate of recurrent ischemia may be due to enhanced thrombogenicity among diabetics, more potent antithrombotic agents may be useful and are being evaluated in clinical studies.

Left ventricular function. Although some investigators (27) regarded left ventricular ejection fraction as a critical determinant for outcome, global left ventricular systolic function was similar between patients with and without diabetes after AMI (21,28). This finding was consistent in both the early and late phase of the in-hospital period. Not surprisingly, other investigators (29) have suggested that left ventricular ejection fraction tended to approach 50% in various treatment groups in large clinical trials, or the "50% rule," which precluded meaningful comparison. There was also no difference in systolic function between diabetic and nondiabetic patients (21,30). Recovery of function of these segments during the late hospitalization period was comparable. In addition, there was no difference in infarct size between these two groups of patients (3). These findings were contrary to the hypothesis that sulfonylurea induced impairment of ischemic preconditioning, which resulted in greater myocardial damage and higher mortality (31–33). Several factors may account for the disparity. Although ischemic preconditioning was well demonstrated in a number of animal and angioplasty models, its significance among humans has been questioned (34,35). Furthermore, the interaction between ATP-sensitive potassium channels and sulfonylureas is complex and varied.

The crucial difference in left ventricular function was that the hyperkinetic response of the noninfarcted areas was attenuated in diabetic patients (21,30). This observation, therefore, may explain, to some extent, the greater mortality (36). During the acute phase of AMI, various pathophysiological changes increase the contractility of the myocardium at the noninfarcted zone. However, this response is impaired among diabetic patients and may be related to endothelial, microcirculation and cellular dysfunction (collectively known as diabetic "cardiomyopathy" [37]), autonomic neuropathy and multivessel disease. After the acute phase of AMI, and with the resolution of the abnormal pathophysiological stresses, the myocardial response at the noninfarct zone normalizes, and contractility was similar between diabetic and nondiabetic patients (21).

MECHANICAL REPERFUSION STRATEGIES

The advent of percutaneous transluminal coronary angioplasty (PTCA) has broadened the horizon for the treatment

of coronary artery disease. With reocclusion of the infarct artery as a major problem fibrinolysis for AMI, the TIMI II (38) trial randomized 3,339 patients to an invasive or conservation strategy. All patients were treated with tissue-plasminogen activator. Those receiving the invasive strategy underwent coronary angiography within 18 to 48 h of randomization, and PTCA was performed on the infarct artery when the anatomy was appropriate. Otherwise, coronary artery bypass grafting was recommended. In contrast, patients randomized to the conservative strategy underwent these procedures only when there was spontaneous or provoked myocardial ischemia. Among patients with diabetes, the 42-day mortality was substantially higher for those in the invasive strategy (14.8% vs. 4.2%; $p < 0.001$). Conversely, there was no difference in mortality among nondiabetic patients randomized to invasive or conservative strategies (3.8% vs. 3.4%), and, hence, the investigators cautioned the use of the invasive approach for patients with diabetes.

With improvement in techniques and operator experience, primary angioplasty for the treatment of AMI has been shown to improve outcome compared with fibrinolytic therapy (39) by early and complete restoration of antegrade flow. The expanded lumen, as compared with fibrinolytic therapy, also resulted in lower rates of recurrent ischemia (28). In a subanalysis of one of these trials (40), survival among patients with diabetes was improved after primary angioplasty. But the effect was attributed to the greater number of older patients. More recently, the preliminary results of 159 patients with diabetes who underwent direct angioplasty for AMI were encouraging (41). The initial success rate was high (98%) with low in-hospital event rates and short hospital stay (mean of 2.7 days). At the end of 12 months, mortality was 2.2% and reinfarction was 9%, and 86% of patients were free of adverse events. However, more rigorous application of this therapeutic intervention afforded only modest benefit (42), regardless of diabetic status (43), and, hence, its application requires further evaluation.

Coronary stenting has improved the results of PTCA (44,45). Primary stenting for AMI has also been shown to be superior to conventional balloon angioplasty (46–48). Therefore, this approach may be appropriate for patients with diabetes. In a small series of 104 patients (49), the immediate angiographic results of patients with AMI who underwent coronary stenting were similar between patients with and without diabetes. However, patients with diabetes have a substantially higher rates of stent thrombosis (18% vs. 1%; $p = 0.003$). At the end of a year, survival was considerably lower among patients with diabetes (89% vs. 99%; $p = 0.04$). However, GP IIb/IIIa inhibitors, which were not routinely used in this study, may improve outcomes of this high-risk group of patients.

IMPAIRED GLUCOSE UTILIZATION

During periods of increased workload (50) or ischemia (51), glucose tends to undergo anaerobic metabolism. To maintain myocardial function, uptake of glucose has to be increased (52) by a process facilitated by the principal transporter, GLUT4. When there is insulin deficiency, GLUT-4 translocation is correspondingly reduced, and there is a shift towards fatty acid metabolism, which is rapidly generated from increased sympathetic activity (53). These aberrations result in increased oxygen consumption and subsequent deterioration of myocardial function. Furthermore, free fatty acids (FFA) may reduce contractility, and subsequent production of free radicals will lead to membrane instability and promote arrhythmias (54). This vicious cycle will result in loss of membrane integrity and eventual cell death.

The basis for the use of glucose insulin potassium (GIK) solution for the treatment of AMI may be related to myocardial protection, in particular, before and after reperfusion (55). With the availability of exogenous glucose, insulin and potassium, adenosine triphosphate (ATP) is generated more efficiently and lipolysis is inhibited and, hence, lowers the amount of FFA (56).

By pooling the results of nine early studies, administration of GIK resulted in a laudable 28% lowering of in-hospital mortality among 1,932 patients (57). Indeed, when the concentration of GIK was sufficiently high enough to suppress fatty acid levels in four of these trials, there was a substantial 48% mortality reduction. To further complicate the issue, the preliminary results of a Polish clinical trial consisting of 954 patients randomized to 24-hour infusion of low-dose GIK or saline cast doubt again on the efficacy of this therapy. Total mortality rates were considerably higher among those receiving GIK at 35 days (8.9% vs. 4.8%; $p = 0.01$) and six months (11.1% vs. 6.5%; $p = 0.01$) (58). There was no significant difference in cardiac mortality or events. The lack of beneficial effect may be related to the dose and duration of GIK infusion.

In the Diabetic Patients with Acute Myocardial Infarction (DIGAMI) Study (59), 306 of 620 patients were randomized to receive insulin-glucose infusion followed by multidose subcutaneous insulin and the remaining 314 patients to conventional therapy. At three months, the level of glycosylated hemoglobin was lower than the control group (7% vs. 7.5%; $p < 0.01$). By the end of the first year, there was a 29% reduction in mortality. The benefit, amounting to lowering mortality by 52%, was greatest among patients with low cardiovascular risk profile and no previous insulin treatment. Although these results are extremely encouraging, validation from a prospective adequately powered clinical trial using current techniques would be required before this treatment strategy could be widely adopted.

Conclusions. Through a variety of direct and indirect pathophysiological mechanisms, patients with diabetes are associated with a substantially worse outcome after AMI, even in this current era of fibrinolysis. This observation could not be explained by the patency response to fibrinolytic agents. In fact, survival benefit was similar in patients with and without diabetes when treated with accelerated tissue plasminogen activator compared with streptokinase (3). More potent fibrinolytic agents will likely achieve similar infarct vessel reperfusion rates between diabetic and nondiabetic patients. An important clinical difference is the rate of recurrent ischemia (3). More potent antithrombotic agents are likely to further improve outcomes of these patients.

Another crucial concept in the management of patients with AMI is to keep the infarct artery open to afford better survival. Although patency of the infarct artery could be rapidly achieved with PTCA, routine revascularization of patients with diabetes receiving fibrinolytic therapy may be detrimental. On the other hand, PTCA is likely to improve survival of patients with recurrent ischemia, especially when left ventricular systolic function is impaired (60). Direct angioplasty may provide similar survival benefit for patients with and without diabetes, particularly with the concomitant use of coronary stenting and GP IIb/IIIa inhibition.

Beyond restoring infarct-artery reperfusion, other strategies of preserving myocardial and correcting metabolic derangements during the peri-infarctional period may further improve outcome. These promising treatment modalities are being evaluated in clinical studies. Whether the use of sulfonylureas is associated with adverse outcomes among patients with diabetes remains uncertain (61).

Among diabetic patients, the process of atherosclerosis is more diffuse (21). Cardiovascular mortality among patients with type II diabetes without prior MI was reported to be as high as nondiabetic patients with previous infarction in a seven-year follow-up Finnish study (62). Therefore, aggressive risk factor modification strategies, even in the absence of established coronary heart disease, should be adopted early. In conclusion, despite substantial advances in the treatment of AMI over the past several years, effective therapeutic modalities are still desperately needed to improve the outcomes of this high-risk group of patients.

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Reprint requests and correspondence: Dr. Eric J. Topol, Department of Cardiology, F25, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44195. E-mail: topole@ccf.org.

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