

Combined Glycoprotein IIb/IIIa Inhibitors and Fibrinolytics

Outcome of Acute ST-Segment Elevation Myocardial Infarction in Diabetics Treated With Fibrinolytic or Combination Reduced Fibrinolytic Therapy and Platelet Glycoprotein IIb/IIIa Inhibition

Lessons From the GUSTO V Trial

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OBJECTIVES	We studied the outcome of diabetics enrolled in the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) V trial to assess whether the combination of half-dose reteplase and abciximab provides any propitious benefits over standard fibrinolytic therapy in diabetic patients.
BACKGROUND	Diabetics with acute ST-segment elevation myocardial infarction (MI) have a worse outcome compared with nondiabetics. Higher-risk patients are usually more likely to benefit from advances in medical therapy.
METHODS	We analyzed diabetic patients enrolled in the GUSTO V trial to assess the outcome of those randomized to the combination of half-dose reteplase and abciximab versus those randomized to reteplase. We also evaluated whether any differences existed in presentation and outcome of MI among the diabetics versus the nondiabetics enrolled in the study.
RESULTS	The trial enrolled 13,782 nondiabetics and 2,633 diabetics. Compared to nondiabetics, diabetics had a significantly higher mortality at 30 days (8.5% vs. 5.1%, $p < 0.001$) and at 1 year (12.7% vs. 7.5%, $p < 0.001$). Among the diabetic subset, no significant difference existed in the incidence of 30-day (8.8% vs. 8.2%, $p = 0.52$) or 1-year mortality (13.0% vs. 12.4%, $p = 0.62$) among patients randomized to reteplase compared to those receiving combination of abciximab and reteplase. The incidence of reinfarction (2.5% vs. 4.3%, $p = 0.013$), recurrent ischemia (11.8% vs. 14.9%, $p = 0.017$), and urgent revascularization (10.9% vs. 13.3%, $p = 0.055$) at seven days was lower in diabetics treated with the combination therapy.
CONCLUSIONS	Compared to nondiabetics, diabetics continue to have a worse outcome with MI. Although combination therapy did not provide a survival benefit, nonfatal ischemic outcomes, including reinfarction, recurrent ischemia, and urgent revascularization, were substantially reduced. (J Am Coll Cardiol 2004;43:542-8) © 2004 by the American College of Cardiology Foundation

Diabetes is a major health problem, with over 7% of the U.S. population afflicted with the disease (1). Cardiovascular disease is the leading cause of mortality and morbidity in the diabetic population (2). Diabetes not only imparts a greater risk of myocardial infarction (MI) but is also associated with a worse short- and long-term outcome after an MI (3,4).

Several encouraging pilot studies suggested earlier and

improved myocardial reperfusion in patients presenting with MI treated with combined half-dose plasminogen activator and platelet glycoprotein (GP) IIb/IIIa antagonists (5,6). Diabetics have evidence of increased platelet reactivity (7-9) and appear to derive an enhanced benefit from GP IIb/IIIa platelet receptor antagonists (10-12). The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) V was a large-scale randomized trial designed to detect a mortality difference between standard fibrinolytic therapy and the combination of reduced-dose fibrinolytic and abciximab in patients presenting with acute ST-segment elevation MI (13). Combination therapy did not significantly reduce mortality in that trial, although rates of reinfarction and urgent revascularization were significantly diminished. The objective of our study was to determine if diabetic patients

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Abbreviations and Acronyms

ACE	=	angiotensin-converting enzyme
CI	=	confidence interval
ECG	=	electrocardiogram/electrocardiographic
GP	=	glycoprotein
GUSTO	=	Global Use of Strategies to Open Occluded Coronary Arteries trial
IV	=	intravenous
MI	=	myocardial infarction
OR	=	odds ratio
PCI	=	percutaneous coronary intervention

have a different pattern of benefit from combination therapy compared with nondiabetics. Furthermore, we compared the diabetic population enrolled in GUSTO V with those enrolled in the previous GUSTO I and GUSTO III trials to study the appropriate use of adjunctive therapies and outcome of diabetics over the last decade.

METHODS

The design and results of GUSTO V have been previously reported (13). In the GUSTO V trial, 16,588 patients with ST-segment elevation MI were randomly assigned between July 1999 and February 2001 to receive reteplase (two 10-U boluses 30 min apart) or the combination of abciximab (infusion of 0.25 mg/kg bolus and 0.125 μ g/kg/min, [maximum of 10 μ g/min] infusion for 12 h) plus half-dose reteplase (two boluses of 5 U, 30 min apart). All patients were given aspirin. The participating investigator determined the use of all other adjunctive medications.

The primary end point of the GUSTO V study was all-cause mortality at 30 days. Reinfarction was defined by prolonged chest pain associated with new significant electrocardiographic (ECG) changes, an increase in cardiac enzyme concentration, or both. Recurrent ischemia was defined as symptoms lasting >5 min, ECG changes, and/or new hypotension, pulmonary edema or murmur, believed by the physician to represent myocardial ischemia without ECG, or enzymatic evidence of infarction. These and all other complications of acute MI were prospectively defined and recorded for all patients until day 7 or hospital discharge (whichever was earlier). Percutaneous revascularization was recorded as urgent if defined so by the investigator. Bleeding was classified as severe when associated with hemodynamic compromise, moderate when requiring transfusion without hemodynamic compromise, and mild without transfusion or hemodynamic compromise. Diabetes was defined on the basis of patient report.

The design and outcome of GUSTO I and GUSTO III trials have been previously described (14,15). The GUSTO I trial randomized 41,021 patients between December 1990 and February 1993 to four different thrombolytic strategies: streptokinase and subcutaneous heparin; streptokinase and intravenous (IV) heparin; accelerated tissue plasminogen

activator (t-PA) and IV heparin; or a combination of streptokinase plus t-PA with IV heparin (14). All patients received aspirin and beta-blockers (if not contraindicated), whereas use of other adjunctive medications was at the discretion of the treating physician. The GUSTO III trial randomized 15,059 patients between October 1995 and January 1997 with acute ST-elevation MI to accelerated t-PA or reteplase (15). All patients received aspirin and IV heparin. Use of all other adjunctive medications was determined by the treating physician. To compare outcome and presentation across GUSTO I, GUSTO III, and GUSTO V trials, we included patients from the 11 countries that were common to the three trials (Australia, Belgium, Canada, France, Germany, United Kingdom, Netherlands, Poland, Spain, Switzerland, and the U.S.).

Statistical analysis. Baseline characteristics were summarized by the use of frequencies and percentages for categorical factors and means and standard deviation for continuous factors. Differences in baseline characteristics were tested with Pearson chi-square tests for categorical factors and Wilcoxon rank-sum tests for continuous variables. Multivariable logistic models were used to estimate the adjusted odds of 30-day death for the diabetic population. Spline transformations were used for pulse rate and blood pressure and logarithmic transformation for time from symptom onset to study drug. The interactions between various variables were explored, and the significant interaction terms incorporated in the model. A value of $p < 0.05$ was used as the level for statistical significance. The SAS version 6.12 (SAS Inc., Cary, North Carolina) was used as the statistical software.

RESULTS

GUSTO V. The GUSTO V trial enrolled 13,782 nondiabetics and 2,633 diabetics. The baseline characteristics of the diabetics and nondiabetics are shown in Table 1. Diabetics tended to be older and included a greater percentage of women and minorities as compared with nondiabetics. They were more likely to have hypertension, hypercholesterolemia, peripheral vascular disease, and prior history of MI and coronary revascularization. They were less likely to have a family history of premature coronary artery disease or to be current smokers. Further, diabetics were more likely to present late after onset of symptoms, to have anterior MI, and to have a higher heart rate and a worse Killip class at presentation. The 30-day mortality was significantly higher in diabetics (Table 2), and there was a trend toward a greater incidence of reinfarction. Diabetics had a significantly higher mortality at one year compared to nondiabetics (12.7% vs. 7.5%, $p < 0.001$).

Table 3 describes the characteristics of the diabetic patients randomized to reteplase versus combination therapy. The groups were evenly matched, with a slightly greater mean age in the group randomized to combination therapy. In concordance with the overall cohort of the trial, there was

Table 1. Baseline Characteristics of Patients Enrolled in GUSTO V Based on Diabetes

	Nondiabetic (n = 13,782)	Diabetic (n = 2,633)	p Value
Age (mean yrs)	61 ± 12	64 ± 11	<0.001
Age >75 yrs	13% (1,797)	16% (422)	<0.001
Female	23.2% (3,193)	32.2% (848)	<0.001
Current smoker	48.5% (6,631)	32.1% (835)	<0.001
Body mass index (mean)	26.79 ± 4.03	28.38 ± 4.72	<0.001
Caucasian	96.6% (13,774)	93.6% (2,632)	<0.001
Treated hypertension	30.4% (4,172)	51.9% (1,357)	<0.001
Treated hypercholesterolemia	15.2% (2,049)	26.1% (658)	<0.001
Family history of early CAD	31.2% (3,815)	27.1% (601)	<0.001
History of PVD	4.6% (582)	8.3% (195)	<0.001
Previous history of MI	14.2% (1,943)	20.9% (540)	<0.001
Prior PCI	6.2% (846)	9.3% (241)	<0.001
Prior CABG	3.0% (415)	4.9% (127)	<0.001
Anterior MI	36.9% (5,085)	40.0% (1,052)	<0.001
Mean systolic blood pressure at presentation (mm Hg)	134 ± 23	138 ± 24	0.01
Mean heart rate at presentation	74 ± 17	79 ± 19	<0.001
Killip class			<0.001
1	89.4% (12,308)	83.8% (2,204)	
2	9.2% (1,269)	13.2% (347)	
3	0.9% (122)	2.3% (60)	
4	0.5% (63)	0.7% (18)	

CABG = coronary artery bypass grafting; CAD = coronary artery disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease.

no difference in the 30-day or one-year mortality among diabetics randomized to the two arms of GUSTO V (Fig. 1). A significant decrease occurred in the number of patients developing reinfarction or recurrent ischemia (Table 4) and a trend toward a decrease in the need for urgent revascularization with the combination of abciximab and half-dose reteplase. Use of combination therapy was associated with a significant reduction in the composite of death, MI, recurrent angina, or ischemia and revascularization at seven days (odds ratio [OR] 0.83, 95% confidence interval [CI] 0.71 to 0.97, $p = 0.021$) and the composite of MI, recurrent angina or ischemia and revascularization at seven days (OR 0.81, 95% CI 0.69 to 0.95, $p = 0.008$). Furthermore, patients randomized to the combination therapy were overall less likely to develop complications of MI (Table 4). Although no difference was seen in the incidence of mechanical complications or heart failure, ventricular tachyarrhythmias were less likely in patients receiving the combination therapy. And even though combination therapy was associated with excess risk of bleeding, no increases in intracranial bleeding rate or blood transfusion occurred with this regimen.

Table 5 depicts the major predictors of 30-day mortality in diabetics. The model had a c statistic of 0.83, suggesting good discrimination. Four easily identifiable variables (age, heart rate, systolic blood pressure, and Killip class) provide almost 85% of the prognostic information with respect to hazard of 30-day mortality.

Compared with nondiabetics, the diabetics enrolled in GUSTO V were more likely to receive angiotensin-converting enzyme (ACE) inhibitors (67.3% vs. 56.5%, $p < 0.001$), calcium channel blockers (11.6% vs. 9.1%, $p = 0.001$), digoxin (7.9% vs. 5.1%, $p = 0.001$), inotropic agents (9.9% vs. 7.6%, $p = 0.001$), and nitrates (75.3% vs. 71.6%, $p = 0.001$). They were less likely to receive aspirin (93.2% vs. 94.9%, $p = 0.002$); little difference was noted in the use of beta-blockers (83.5% vs. 84.9%, $p = 0.116$).

Diabetics in GUSTO I, GUSTO III, and GUSTO V. To compare outcome and adjunctive medication use among diabetics over the last decade, we compared 5,376 diabetics in GUSTO I, 1,886 in GUSTO III, and 1,938 in GUSTO V enrolled in the 11 common countries. There was a trend toward an improvement in survival across the

Table 2. Outcome of Patients Enrolled in GUSTO V Based on Diabetic Status

	Nondiabetic (n = 13,782)	Diabetic (n = 2,633)	p Value
Death at 30 days	5.1% (709)	8.5% (223)	<0.001
Reinfarction within 7 days	2.8% (385)	3.4% (90)	0.08
Urgent CABG or PCI within 7 days	12.1% (1,665)	12.1% (318)	0.996
Death, MI, or urgent revascularization within 7 days	16.8% (2,315)	19.0% (499)	0.007
Death at 1 year	7.5% (1027)	12.7% (334)	<0.001

Abbreviations as in Table 1.

Table 3. Baseline Characteristics of Diabetic Patients Enrolled in GUSTO V Based on Treatment Arm

	Reteplase (n = 1,299)	Reteplase + Abciximab (n = 1,334)	p Value
Age (mean yrs)	64 ± 11	65 ± 11	0.04
Age >75 yrs	15.8% (205)	16.3% (217)	0.73
Female	32.5% (422)	31.9% (416)	0.76
Current smoker	32.6% (419)	31.6% (416)	0.57
Body mass index (mean)	28.38 ± 4.74	28.38 ± 4.70	0.90
Caucasian	93% (1,207)	94.2% (1,257)	0.16
Treated hypertension	51.1% (658)	52.6% (699)	0.46
Treated hypercholesterolemia	26.4% (328)	25.8% (330)	0.72
Family history of early CAD	28.3% (312)	26.0% (289)	0.24
History of PVD	7.3% (84)	9.4% (111)	0.06
Previous history of MI	20.4% (260)	21.4% (280)	0.51
Prior PCI	9.2% (118)	9.3% (123)	0.91
Prior CABG	4.3% (55)	5.4% (72)	0.16
Anterior MI	40.5% (526)	39.4% (526)	0.56
Mean systolic blood pressure at presentation (mm Hg)	138 ± 24	138 ± 23	0.72
Mean heart rate at presentation	79 ± 19	79 ± 19	0.60
Killip class			0.058
1	84.2% (1,091)	83.5% (1,113)	
2	13.3% (172)	13.1% (175)	
3	2.1% (27)	2.5% (33)	
4	0.5% (6)	0.9% (12)	

Abbreviations as in Table 1.

last decade (Table 6) although no improvement in survival of patients presenting in Killip class 3 and class 4 was noted. Furthermore, there was a greater utilization of appropriate adjunctive therapies in these patients, as seen in the increased use of beta-blockers and ACE inhibitors.

DISCUSSION

Data from the three GUSTO trials corroborate and extend previous evidence that, compared to nondiabetics, diabetics have worse outcome after MI. The large number of diabetics enrolled in GUSTO V provide a unique opportunity to study the impact of this disease on the morbidity and

mortality associated with MI. Compared to nondiabetics, diabetics continue to present with a higher Killip class and have a worse outcome with MI. Although combination therapy did not provide a survival benefit, it was associated with a reduction in the incidences of reinfarction, recurrent ischemia, and urgent revascularization.

Diabetes is a rapidly growing health problem, with approximately 4% of adults being diabetics worldwide (16). The epidemic appears to be accelerating, with a projected 300 million diabetics by the year 2025 (16). Cardiovascular disease is a major cause of mortality and morbidity in diabetics, and multiple studies have suggested a markedly

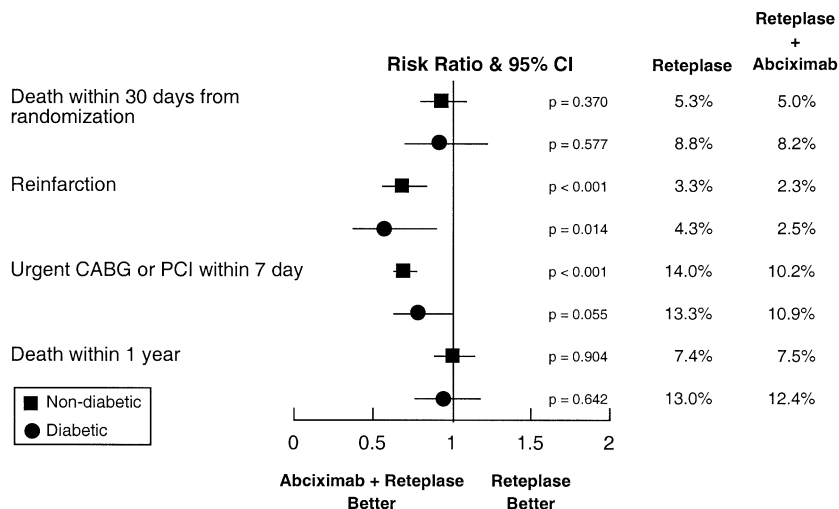


Figure 1. Outcome of diabetics with myocardial infarction randomized to standard versus combination therapy. CABG = coronary artery bypass grafting; CI = confidence interval; PCI = percutaneous coronary intervention.

Table 4. Complications of MI and its Treatment in Diabetics Randomized to Standard Versus Combination Therapy

	Retepase (n = 1,299)	Retepase + Abciximab (n = 1,334)	p Value
Any complication of index MI	35.8% (465)	30.0% (400)	0.002
Reinfarction	4.3% (56)	2.5% (34)	0.013
Recurrent ischemia/angina	14.9% (194)	11.8% (157)	0.017
Composite of 7-day death, MI, recurrent ischemia/angina or revascularization	44.99% (584)	40.54% (540)	0.021
Composite of 7-day MI, recurrent ischemia/angina or revascularization	40.76% (529)	35.74% (476)	0.008
New severe CHF	6.6 (86)	7.0 (93)	0.721
Myocardial rupture	0.6% (8)	0.7% (9)	0.851
Ventricular septal defect	0.3% (4)	0.2% (3)	0.722
Sustained ventricular tachycardia	3.2% (42)	1.9% (26)	0.038
Ventricular fibrillation	3.6% (47)	2.1% (28)	0.019
Atrial fibrillation	5.1% (66)	4.5% (60)	0.483
Asystole	2.7% (35)	3.2% (43)	0.423
2nd or 3rd degree heart block	3.5% (45)	2.5% (34)	0.169
Intracranial hemorrhage	1.0% (13)	0.6% (8)	0.004
Any bleeding	14.2% (184)	26.7% (356)	<0.001
Blood transfusion	5.5% (71)	6.5% (86)	0.288

CHF = congestive heart failure; MI = myocardial infarction.

worse outcome in diabetics presenting with ST-segment elevation or non-ST-segment elevation MI (3,4).

Recent evidence points to emergence of platelets as key mediators in acute coronary syndromes (17). Diabetics have evidence of increased platelet activation (7), adhesiveness and aggregability (8), and greater expression of platelet GP IIb/IIIa, thrombospondin, and P selectin (9). Based on these lines of evidence, potent platelet inhibition may be of particular benefit in diabetic patients presenting with acute coronary syndromes. While all subjects appeared to benefit from peri-procedural abciximab, the diabetic substudy of Evaluation of platelet IIb/IIIa inhibitor for stenting trial (EPISTENT) suggested an enhanced outcome in diabetics randomized to abciximab (11). Combined analysis from three major percutaneous coronary intervention (PCI) trials suggested a marked one-year mortality benefit of abciximab in diabetics undergoing PCI (12). Similar enhanced benefits of tirofiban in diabetics have been reported in the setting of acute coronary syndromes (18). Roffi et al. (10) performed a

meta-analysis of all major trials of platelet GP IIb/IIIa inhibitors in non-ST-segment elevation acute coronary syndrome and described a reduction in 30-day mortality in diabetics from 4.0% to 1.2% ($p = 0.002$). This improved outcome in diabetics in PCI and acute coronary syndromes raises the question of possible enhanced benefit for diabetics in the setting of ST-segment elevation MI as well.

The randomized design and the large number of diabetic patients enrolled in GUSTO V provided an almost matched population in the two arms. In parallel with the main trial, no significant mortality difference was noted between patients treated with reteplase or combination therapy. However, the consistent reductions in reinfarction, recurrent ischemia, urgent revascularization, and malignant ventricular arrhythmias as seen in the main trial suggest additional benefits of enhanced platelet suppression achieved using combination therapy. Fibrinolytic agents lyse fibrin-thrombin clot and release free thrombin, which is a potent stimulator of platelet aggregation (19).

Table 5. Predictors of 30-Day Mortality in Diabetics in a Multivariable Model

	Odds Ratio	95% CI	Chi-Square	p Value
Age (yrs)	1.073	1.052-1.094	49.764	<0.001
SBP (<115 mm Hg)*	0.969	0.950-0.989	9.165	0.003
SBP (\geq 115 mm Hg)*	0.972	0.962-0.983	26.986	<0.001
Pulse (<58/min)†	1.000	0.939-1.064	0	1.000
Pulse (>58/min)†	1.023	1.014-1.032	26.343	<0.001
Killip class III and IV	4.638	2.537-8.479	24.848	<0.001
Anterior infarct	1.584	1.123-2.234	6.863	0.009
History of PVD	1.772	1.088-2.887	5.287	0.022
Current smoker	0.552	0.334-0.887	6.029	0.014
Weight >90 kg	0.538	0.327-0.884	5.984	0.014

*Systolic blood pressure (SBP) had a varying effect on mortality hazard. Each 1 mm Hg rise was associated with a greater proportional reduction in the hazard of mortality below an SBP of 115 mm Hg compared to a somewhat lesser reduction in hazard above an SBP of 115 mm Hg. †A rising pulse was associated with an increasing hazard of mortality above a heart rate of 58. No relationship was seen between mortality and a heart rate lower than 58.

CI = confidence interval; PVD = peripheral vascular disease.

Table 6. Outcome and Medication Use in Diabetics in GUSTO I, GUSTO III, and GUSTO V

Diabetic Subset	GUSTO I (1990-1993)	GUSTO III (1995-1997)	GUSTO V (1999-2001)	p Value
Diabetics/total	5,376/37,110 (14.5%)	1,886/11,996 (15.7%)	1,938/12,603 (15.4%)	
Death (30 days)	10.7%	10.9%	8.9%	0.06
30 day-mortality (Killip class I and II)	9.3%	9.6%	7.5%	0.04
30-day mortality (Killip class III and IV)	44.5%	44.1%	50.0%	0.722
Beta-blocker use	75.1%	75.7%	83.5%	<0.001
ACE inhibitor use	28.9%	54.9%	67.3%	<0.001
Aspirin use	98.1%	98.6%	93.2%	<0.001

ACE = angiotensin-converting enzyme.

Combination therapy would hence be expected to specifically impact on the platelet-mediated recurrent ischemic events and distal embolization. Indeed, the current data support the previously described reduction in clinical events and improved tissue level perfusion with combination therapy (5,20). These improvements in key complications of MI are at the cost of an increase in mild and moderate bleeding. However, the need for transfusions or the incidence of intracranial hemorrhage was not higher in the combination arm, hence suggesting an acceptable safety profile.

These findings are in contrast to those from the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-III study (21), which suggested a worse outcome among diabetic patients receiving half-dose tenecteplase and abciximab combination therapy compared to those receiving tenecteplase and heparin. These results from ASSENT-III are probably a reflection of the small number of diabetics in that study (355 in the combination therapy arm versus 363 in the unfractionated heparin plus tenecteplase arm and 380 in the enoxaparin plus tenecteplase arm) and may exemplify a type I statistical error. Alternatively, these differences may relate to the different agents used or differences in the patients enrolled and are best delineated in an adequately powered prospective study.

Previous experience with abciximab in the setting of primary PCI for ST-segment elevation MI has been even more encouraging. The small number (53) of diabetics enrolled in the Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up (ADMIRAL) trial who received abciximab in the setting of stenting for ST-segment elevation MI had a significant reduction in the six-month mortality rate as compared with those randomized to placebo (0% vs. 16.7%, $p = 0.02$) (22). Further, a significant reduction occurred in the composite of death, reinfarction, or any revascularization. Reminiscent of the data in acute coronary syndrome, the benefit of abciximab appeared to be enhanced in diabetics compared to nondiabetics. The lack of similar findings in GUSTO V may suggest vital difference in the role of abciximab in the setting of two differing strategies of reperfusion. Whereas more evidence supports the efficacy of such therapy in primary PCI, the lack of mortality benefit with combination therapy makes its rou-

tine use less compelling and suggests a need for further research to clarify its role in clinical practice.

Compared with the GUSTO I and GUSTO III trials, GUSTO V was marked by an improvement in 30-day survival after MI. This improvement was seen in both diabetics and nondiabetics and may represent temporal trends in improved therapy or differences in type of enrolled patients. A comparison of diabetics and nondiabetics suggests a worse outcome in diabetics in concordance with previous work. The key predictive variables of outcome in diabetics were similar to those in the nondiabetic population. Heart rate and blood pressure retained a major predictive role in this population despite the theoretical concerns of dysautonomia.

Concern has been raised that diabetics are less likely to receive appropriate adjunct therapy following an MI. Using the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) Augsburg registry, Lowel and colleagues (23) found marked underutilization of beta-blockers during hospitalization and at discharge in diabetics. McGuire et al. (3) also described a lower use of beta-blockers (68.4% vs. 72.4%, $p = 0.001$) in diabetics compared with nondiabetics in the GUSTO-IIb study. Concerns about masking of hypoglycemia in diabetics may have been responsible in part for the underutilization of such proven therapy. In GUSTO V, diabetics and nondiabetics were equally likely to receive beta-blockers, whereas diabetics were actually more likely to receive angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, and digoxin. This may reflect the increased awareness of benefits of ACE inhibitors in diabetics and the increased prevalence of hypertension and congestive heart failure in this group. A comparison across GUSTO I, GUSTO III, and GUSTO V shows an appropriate increase in use of beta-blockers and ACE inhibitors in diabetics. The use of aspirin decreased somewhat and could not be accounted for by increased bleeding complications, randomization arm, or use of adenosine diphosphate antagonists, the latter being used in only a small minority of aspirin nonusers (data not shown). This increased utilization of the appropriate and proven therapies may directly contribute to or may be a marker of better overall care, which in turn

might conceivably have led to the improvement seen in outcome of diabetics in GUSTO V.

Study limitations. Our analysis was a retrospective subgroup analysis, and hence it is subject to the known limitations regarding sample size and spurious findings inherent in such work. Diabetes was defined by patient report and may have led to significant underreporting of diabetes. No data on HbA_{1c} or blood glucose at presentation were available. Further, time to ST-segment resolution was available only in a small number of diabetics, thus precluding study of effect of combination therapy on microvascular perfusion. The diabetic substudy was underpowered to detect a mortality difference at 30 days, although our findings parallel those of the main trial and thus are likely to be extant. These findings should be considered hypothesis generating and hence require validation in prospective studies.

Differing enrollment criteria, varying practice patterns, and evidence base and different therapeutic agents being tested limit the comparison of diabetics across the three GUSTO trials. We have accordingly limited our analysis to provide general information about use of adjunctive therapies as a barometer of practice patterns across similar centers over the last decade.

Conclusions. Diabetes continues to be associated with a worse outcome after ST-segment elevation MI, in part owing to the more serious associated co-morbidities and partly due to a worse clinical presentation. There has been an improvement in outcome and use of appropriate adjunct therapy in diabetics when compared to historical controls. As in nondiabetics, combination therapy appears to reduce the risk of recurrent ischemia, reinfarction, need for revascularization, and ventricular tachyarrhythmias in diabetics without any improvement in either short- or long-term mortality. Although the improvement in secondary end points with combination therapy provides a small step forward, the continued high short- and long-term mortality reinforces the significance of the burden associated with a common and growing public health problem.

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