Type 2 Diabetes and Intravenous Thrombolysis Outcome in the Setting of ST Elevation Myocardial Infarction

MICHAEL N. ZAIRIS, MD
ANASTASSIOS G. LYRAS, MD
STAMATIS S. MAKRYGIANNIS, MD
PARASKEVI K. PSAROGIANNI, MD
EVDOKIA N. ADAMOPOULOU, MD
STELIOS M. HANDANIS, MD
APOSTOLOS PAPANTONAKOS, MD
SPYROS K. ARGYRAKIS, MD
ATHANASIOS A. PREKATES, MD
STEFANOS G. FOUSSAS, MD

OBJECTIVE — There are conflicting results regarding the impact of type 2 diabetes on intravenous thrombolysis effectiveness during ST elevation myocardial infarction (STEMI). The present study, using a continuous 12-lead electrocardiogram, examined the possible association of type 2 diabetes with both acute intravenous thrombolysis effectiveness and long-term prognosis in this setting.

RESEARCH DESIGN AND METHODS — The study included 726 consecutive subjects (214 type 2 diabetic subjects) with STEMI who received intravenous thrombolysis in the first 6 h from index pain and were followed up for 3.5 years.

RESULTS — Type 2 diabetic subjects had significantly lower incidence of sustained ≥50% ST recovery than nondiabetic subjects ($P = 0.03$). Additionally, the former required a significantly greater time interval through the achievement of this criterion than the latter ($P < 0.001$). In both type 2 diabetic ($P < 0.001$) and nondiabetic subjects ($P < 0.001$), those who had not attained ≥50% ST recovery were at significantly higher risk of cardiac death than subjects who had reached this criterion. The subjects who attained the above electrocardiographic criterion in ≥60 min after thrombolysis initiation were at significantly higher risk compared with those who achieved this criterion in <60 min ($P = 0.02$). However, this association was true only for type 2 diabetic subjects ($P = 0.01$) and not for nondiabetic subjects ($P = 0.9$).

CONCLUSIONS — The present study suggests that type 2 diabetes is a strong predictor of acute intravenous thrombolysis failure during STEMI. This finding may significantly contribute to the worse prognosis for type 2 diabetic subjects compared with nondiabetic ones in this setting.

Diabetes Care 27:967–971, 2004

Intravenous thrombolysis administration has significantly reduced cardiac mortality after ST elevation myocardial infarction (STEMI), in both type 2 diabetic and nondiabetic subjects (1). However, even when promptly receiving thrombolysis, the former still fare worse than the latter, manifesting impaired postthrombolysis left ventricular function and prognosis (2,3). Although type 2 diabetic subjects have a worse risk profile, numerous studies have documented that type 2 diabetes exerts an independent adverse effect on the outcome after the acute event (2–4). To evaluate this issue, it has been hypothesized that type 2 diabetes might interfere with acute intravenous thrombolysis effectiveness, as estimated by angiographic or electrocardiographic criteria. Although, several studies have reported similar angiographic (5,6) or electrocardiographic (7,8) success in both type 2 diabetic and nondiabetic subjects, a recent meta-analysis, based on serial snapshot electrocardiograms (ECGs), has shown that the former have less complete resolution of ST elevation than the latter (5).

On the other hand, ST monitoring by continuous 12-lead ECG presents a more accurate and dynamic depiction of the course of tissue-level reperfusion (9,10). The objective of the present study was to investigate the possible association of type 2 diabetes with intravenous thrombolysis outcome in the setting of STEMI using this modality. According to preliminary results (11) of the present study, which integrated only subjects who had attained abrupt and sustained ST recovery within 90 min, type 2 diabetic subjects required almost 50% more time to reach this generally accepted criterion of reperfusion success. In the present report, the final study results are presented.

RESEARCH DESIGN AND METHODS

— The study cohort consisted of 726 consecutive subjects with STEMI who were admitted to our institute and fulfilled the following criteria: *1*) continuous and present upon admission (refractory to nitrates) angina pectoris of ≥30 min duration; *2*) ST elevation of ≥2 mm in ≥2 contiguous precordial leads, or 1 mm in ≥2 contiguous limb leads; and *3*) administration of intravenous thrombolysis in the first 6 h since the index pain. We excluded subjects with type 1 diabetes, left bundle branch block, past coronary bypass surgery, and premature discontinuation of intravenous thrombolysis due to complications. Subjects were considered to be diabetic if they had a previous history of diabetes or a plasma glucose level ≥200 mg/dl on admission or during hospitalization. Subjects were classified as having type 2 diabetes according to the definition of the World Health Organization. The local ethics committee approved the study protocol,

From the Department of Cardiology, Tzanio Hospital, Piraeus, Greece.
Address correspondence and reprint requests to Dr. Michael N. Zairis, 40 Acti Themistocleous St., Piraeus, 18537, Greece. E-mail: zairis@hellasnet.gr.
Received for publication 8 October 2003 and accepted in revised form 23 December 2003.
Abbreviations: ECG, electrocardiogram; ROC, receiver operating characteristic; STEMI, ST elevation myocardial infarction.
© 2004 by the American Diabetes Association.

Table 1 —*Baseline characteristics*

	Nondiabetic subjects	Type 2 diabetic subjects	*P*
n	512	214	
Age (years)	59 ± 10.3	64.2 ± 8.2	<0.001
Male	424 (82.8)	151 (70.6)	<0.001
BMI (kg/m^2)	26.5 ± 2.2	26.8 ± 3.2	0.7
Hypertension	276 (53.9)	123 (57.5)	0.4
Current smoking	334 (65.2)	81 (37.9)	<0.001
Familial CAD	237 (46.3)	101 (47.2)	0.8
Hypercholesterolemia	331 (64.6)	141 (65.9)	0.8
History of stable angina	75 (14.6)	34 (15.9)	0.7
History of myocardial infarction	44 (8.6)	24 (11.2)	0.4
History of coronary angioplasty	58 (11.3)	26 (12.1)	0.8
From index pain to thrombolysis starting (h)	3.5 ± 1.4	3.6 ± 1.4	0.8
Anterior STEMI	312 (60.9)	131 (61.2)	0.9
t-PA	443 (86.5)	185 (86.4)	0.9

Data are means ± SD or *n* (%). CAD, coronary artery disease; t-PA, tissue plasminogen activator.

and informed consent was obtained from all participants.

Treatment

Either streptokinase or tissue type plasminogen activator was used as a thrombolytic agent. Chewed aspirin was administered in a dose of 160–325 mg upon admission and was continued indefinitely. Unfractioned heparin was given as appropriate in a bolus of 60 units/kg (up to 5,000) upon admission, followed by intravenous infusion of 12 units · kg^{-1} · h^{-1} titrated to a therapeutic activated partial thromboplastin time. Heparin was continued in uncomplicated case subjects for 48 h.

Continuous 12-lead ST monitoring

An Eagle 4000 Monitor (GE Marquette Medical Systems, Milwaukee, WI) was connected to each patient immediately after admission to the coronary care unit. ST recording was started with the first acquired ECG (reference ECG) and continued for ≥24 h using the ST Guard system (GE Marquette Medical Systems). The operation of this system has previously been described (10,11). In summary, the software of this system collects ECG waveforms and produces the median QRS-T complexes for the last 10 s of every 1-min period for each of the 12 leads. From these averaged QRS-T complexes, an ST trend curve is constructed for each lead, displayed on a computerized workstation, and stored after eliminating periods of inadequate technical quality. The ST trend of the lead with the higher ST elevation is selected for analysis of ST recovery. During a peak period of ongoing or worsening ST elevation, the reference ECG is continuously updated to the ECG with the most severe ST elevation. In the present study, abrupt and sustained ≥50% ST recovery from the last updated reference ECG, after intravenous thrombolysis initiation, was used to define successful reperfusion. All ST trends were analyzed off-line by one well-trained investigator blinded to the clinical data.

Follow-up

In-hospital and long-term follow-up data were prospectively collected on predesigned forms. Subjects were followed up at 30, 90, and 180 days and every 180 days thereafter for a mean period of 510 ± 334 days (range 1–1,296). Cardiac death was the prespecified primary end point. Cardiac death was defined as sudden unexplained death or death due to fatal myocardial infarction or after rehospitalization because of heart failure or possible acute myocardial ischemia. The diagnosis of cardiac death was verified by death certificates, hospital records, or telephone contact with the subjects' relatives or attending physicians.

Statistical analysis

Values were expressed as means ± SD, and categorical characteristics were expressed as numbers and percentages. Comparisons of continuous variables among the groups were made using ANOVA, Student's *t* test, or the Mann-Whitney *U* test, as appropriate. Associations between two categorical variables were tested using a χ^2 test or Fisher's exact test as appropriate. To evaluate the accuracy of the required time interval through the achievement of abrupt and sustained ≥50 ST recovery, receiver operating characteristic (ROC) curves were constructed in the prediction of the primary end point (measured by the area under the ROC curve, range 0.5–1). To avoid arbitrary cutoff points of the required time to abrupt and sustained ≥50% ST recovery for the prediction of the primary end point, the "optimal" cutoff point with the highest predictive accuracy, which separated the cohort into two populations, was estimated by ROC analysis. Cox's proportional hazard model was used to assess the significance of any noted difference in the incidence of the primary end point between the groups. Event-free survival was analyzed with the Kaplan-Maier method, and log rank was used for comparisons among the curves. All tests were two tailed, and $P < 0.05$ was considered significant. Statistical analysis was performed with SPSS statistical software (release 10.0; SPSS, Chicago, IL).

RESULTS

Baseline characteristics

The mean age of the study subjects was 60.5 ± 10 years (range 28–76). Among the subjects, 575 (575 of 726, 79.2%) were men and 214 (214 of 726, 29.5%) had type 2 diabetes. A total of 443 subjects (443 of 726, 61%) suffered from anterior STEMI, and the mean time interval from index pain to thrombolysis initiation was 3.6 ± 1.4 h (range 0.5–6). Differences between type 2 diabetic and nondiabetic subjects concerning the baseline characteristics are presented in Table 1. Compared with nondiabetic subjects, type 2 diabetic subjects were significantly older and more usually women and nonsmokers.

ST recovery

Intravenous thrombolysis was started in a mean time interval of 9 ± 5 min after subjects' connection to the monitors, with no difference between type 2 diabetic and nondiabetic subjects. There were no statistically significant differences between the two groups regarding either the extent of epicardial ischemia, estimated by the

Table 2 —*Continuous 12-lead ST ECG monitoring*

	Nondiabetic subjects	Type 2 diabetic subjects	*P*
n	512	214	
Altitude of highest ST (mm)	4.6 ± 1.4	4.4 ± 1.2	0.6
Number of leads with ST elevation >1 mm	4.3 ± 1.6	4.2 ± 1.6	0.5
From connection to thrombolysis starting (min)*	8.8 ± 4.9	9.1 ± 5.2	0.6
Subjects with ≥50% ST recovery	261/512 (50.9)	91/214 (42.5)	0.03
Subjects with ≥50% ST recovery in the first 60 min	178/261 (68.2)	31/91 (34.1)	<0.001
Mean time to abrupt and sustained ≥50% ST recovery	50.6 ± 25.4	68.8 ± 27.1	<0.001

Data are means ± SD or *n* (%). *Connection to monitor.

number of leads with >1 mm ST elevation, or the altitude of the highest ST elevation (Table 2). Type 2 diabetic subjects had a significantly lower incidence of abrupt and sustained ≥50% ST recovery than nondiabetic subjects (42.5 vs. 50.9, $P = 0.03$). Additionally, the former required significantly greater time interval until the achievement of this criterion than the latter (68.8 ± 27.1 vs. 50.6 ± 25.4 min, $P < 0.001$, range 11–126 vs. 12–144) (Table 2).

Cardiac mortality

Information concerning cardiac death was obtained in 719 (719 of 726, 99.1%, 505 nondiabetic and 214 type 2 diabetic subjects) patients during the follow-up. The incidence of cardiac death in the entire population was 22.9% (165 of 719), and type 2 diabetic subjects were at significantly higher risk than nondiabetic subjects (38.3 vs. 16.4%, hazard ratio [HR] 2.5, 95% CI 1.8–3.4, $P < 0.001$).

The subjects who had not attained abrupt and sustained ≥50% ST recovery were at significantly higher risk than those who had reached this criterion, and this was true for both type 2 diabetic subjects (47.2 vs. 26.4%, HR 2.4, 95% CI 1.5–3.8, $P < 0.001$) and nondiabetic subjects (22.3 vs. 10.6%, HR 2.3, 95% CI 1.5–3.6, $P < 0.001$).

ROC analysis in the subjects who attained abrupt and sustained ≥50% ST recovery indicated that the time delay until the achievement of this criterion has reasonable accuracy in the prediction of cardiac death (ROC area 0.73, 95% CI 0.62–0.81, $P < 0.001$). The determined optimal cutoff point of this time delay for the prediction of cardiac death was 60 min (Fig. 1). In terms of baseline characteristics, the subjects who achieved sustained ≥50% ST recovery in the first 60 min were similar to those who attained this criterion in ≥60 min after starting thrombolysis. This was true in both type 2 diabetic and nondiabetic subjects. In the entire cohort, the subjects who attained the above ECG criterion in ≥60 min after starting thrombolysis were at significantly higher risk than those who achieved this criterion in <60 min (21 vs. 11.1%, HR 1.9, 95% CI 1.1–3.3, $P = 0.02$). However, subgroup analysis showed that this association was true in type 2 diabetic subjects (33.3 vs. 12.9%, HR 3.1, 95% CI 1.1–9, $P = 0.01$) (Fig. 2*A*) but not in nondiabetic subjects (12 vs. 9.9%, HR 1.1, 95% CI 0.5–2.3, $P = 0.9$) (Fig. 2*B*).

CONCLUSIONS — In our study, type 2 diabetic subjects presented a significantly lower incidence of abrupt and sustained ≥50% ST recovery than nondiabetic subjects after intravenous thrombolysis administration in the setting of STEMI. Additionally, the type 2 diabetic subjects required a significantly prolonged time interval to attain this criterion compared with the nondiabetic subjects. Apart from preliminary results of our study (11), no previous study has focused on the investigation of a possible variation in the course of reperfusion between type 2 diabetic and nondiabetic subjects, exploiting dynamic ST elevation recovery instead of snapshot ECG. The present results are in concordance with a recently published meta-analysis in which it was shown that type 2 diabetic subjects had less frequently complete ST recovery after intravenous thrombolysis administration compared with nondiabetic subjects (5).

A number of possible pathophysiological mechanisms may account for the observed discrepancy in the attainment of ≥50% ST recovery between type 2 diabetic and nondiabetic subjects. Specifically, diffuse coronary artery disease (3,12–14), metabolic derangements (12), complexity of the culprit atherosclerotic

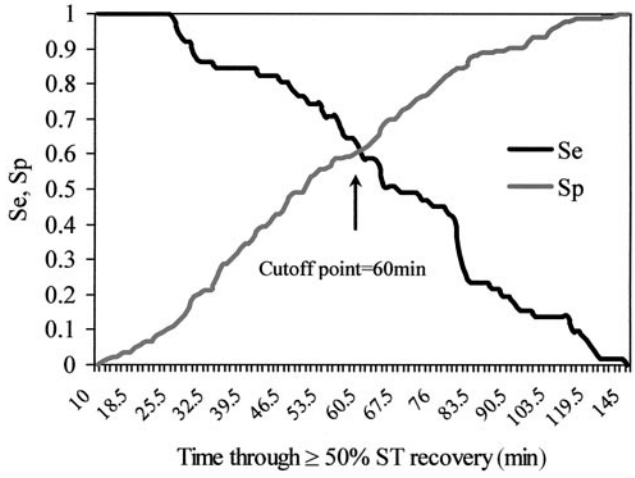

Figure 1—*Optimal cutoff point of the time delay through the attainment of abrupt and sustained ≥50 ST recovery, for the prediction of cardiac death, during the follow-up period. Se, sensitivity, Sp, specificity.*

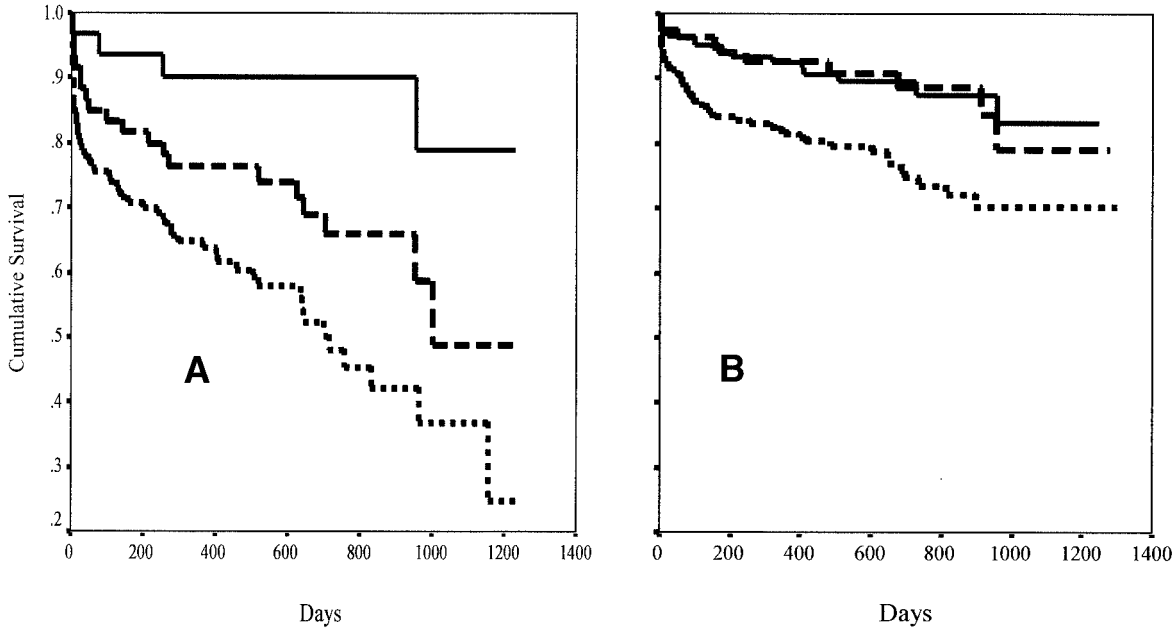

Figure 2—*Kaplan-Maier curves for the incidence of cardiac death among the several subgroups of type 2 diabetic* (A) *and nondiabetic* (B) *subjects during the entire follow-up period, according to the time through the attainment of abrupt and sustained ≥50% ST recovery*. - - -, no ST recovery; – – –, recovery in ≥60 min; ——, recovery in <60 min.

plaque (12,15), microangiopathy (12,16), endothelial dysfunction (12,16), impaired fibrinolysis (16,17), increased platelet aggregatory activity (12,18,19), and diminished flow reserve (16,20,21) may be responsible. Furthermore, certain properties of diabetic blood cells (e.g., reduced cell deformability, alteration of leukocyte function, and a tendency to generate more reactive oxygen species) are also likely to enhance the potential of accumulating in the microcirculation of the heart, causing further danger by an oxygen radical–mediated inflammatory process (22). Diabetes also induces impaired glucose utilization and accumulation of fatty acid intermediates (12,23). Free fatty acids promote ischemic injury through several mechanisms, including direct toxicity, increased oxygen demand, direct inhibition of glucose oxidation, and subsequent production of free radicals that may lead to loss of membrane integrity and eventual cell death (23–25).

According to the present study, although nondiabetic subjects showed no difference in the incidence of cardiac mortality according to the time they achieved satisfactory ST recovery, a remarkable discrepancy was demonstrated among type 2 diabetic subjects. Specifically, type 2 diabetic subjects who attained the aforementioned electrocardiographic criterion beyond 60 min after starting thrombolysis demonstrated significantly higher cardiac mortality than those type 2 diabetic subjects who attained this criterion within the first 60 min. It is possible that the time delay for the attainment of abrupt and sustained ≥50% ST recovery may be more deleterious for diabetic myocardial cells than for nondiabetic ones, resulting in a more compromised postinfarction left ventricular function and prognosis. In any case, the dramatic increase in cardiac mortality of type 2 diabetic subjects, if successful thrombolysis is not attained in the first 60 min after initiation of intravenous thrombolysis administration, may provide reason for a more appropriate therapy in these subjects. Therapeutic approaches that increase and accelerate the achievement of satisfactory reperfusion at the cellular level may further improve prognosis in type 2 diabetic subjects suffering STEMI.

The results of the present study imply that type 2 diabetes is a strong predictor of acute intravenous thrombolysis failure during STEMI. This association may contribute significantly to the worse prognosis of type 2 diabetic subjects compared with nondiabetic ones in this setting. If it is validated with larger prospective studies, more appropriate therapeutic approaches that accelerate and increase the achievement of satisfactory reperfusion in the cellular level may further improve prognosis in type 2 diabetic subjects suffering STEMI.

References

1. The GISSI investigators: Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986; 1:397–401
2. Strandberg LE, Ericsson CG, O'Konor ML, Bergstrand L, Lundin P, Rehnqvist N, Tornvall P: Diabetes mellitus is a strong negative prognostic factor in patients with myocardial infarction treated with thrombolytic therapy. *J Int Med* 248:119–125, 2000
3. Mak KH, Topol E: Emerging concepts in the management of acute myocardial infarction in patients with diabetes mellitus. *J Am Coll Cardiol* 35:563–568, 2000
4. Singer DE, Moulton AW, Nathan DM: Diabetic myocardial infarction: interaction with other preinfarction risk factors. *Diabetes* 38:350–357, 1989
5. Angeja BG, de Lemos J, Murphy SA, Marble SJ, Antman EM, Cannon CP, Braunwald E, Gibson CM, the TIMI Study Group: Thrombolysis in myocardial infarction: impact of diabetes mellitus on epicardial and microvascular flow after fibrinolytic therapy. *Am Heart J* 144:649–656, 2002

6. Woodfield SL, Lundergan CF, Reiner JS, Greenhouse SW, Thompson MA, Rohrbeck SC, Deychak Y, Simoons ML, Califf RM, Topol EJ, Ross AM: Angiographic findings and outcome in diabetic patients treated with thrombolytic therapy for acute myocardial infarction: the GUSTO-I experience. *J Am Coll Cardiol* 28:1661–1669, 1996
7. Mak KH, Moliterno DJ, Granger CB, Miller DP, White HD, Wilcox RG, Califf RM, Topol EJ: Influence of diabetes mellitus on clinical outcome in the thrombolytic era of acute myocardial infarction. *J Am Coll Cardiol* 30:171–179, 1997
8. Ishihara M, Sato H, Kawagoe T, Shimatani Y, Kurisu S, Nishioka K, Kouno Y, Umemura T, Nakamura S: Impact of diabetes mellitus on long term survival after acute myocardial infarction in patients with single vessel disease. *Heart* 86:133–138, 2001
9. Shah A, Wagner GS, Granger CB, O'Connor CM, Green CL, Trollinger KM, Califf RM, Krucoff MW: Prognostic implications of TIMI flow grade in the infarct related artery compared with continuous 12-lead ST-segment resolution analysis. *J Am Coll Cardiol* 35:666–672, 2000
10. Krucoff MW, Croll MA, Pope JE, Granger CB, O'Connor CM, Sigmon KN, Wagner BL, Ryan JA, Lee KL, Kereiakes DJ: Continuous 12-lead ST-segment recovery analysis in the TAMI 7 study: performance of a non-invasive method for real-time detection of failed myocardial reperfusion. *Circulation* 88:437–446, 1993
11. Zairis MN, Makrygiannis SS, Papadaki OA, Lyras AG, Kouzanidis JP, Ampartzidou OS, Handanis SM, Argyrakis SM, Foussas SG: Diabetes and ST elevation myocardial infarction: how successful is intravenous thrombolysis for the diabetic heart? (Letter). *Diabetes Care* 25:1890–1891, 2002
12. Aronson D, Rayfield EJ, Chesebro JH: Mechanisms determining course and outcome of diabetic patients who have had acute myocardial infarction. *Ann Intern Med* 126:296–306, 1997
13. Mosseri M, Nahir M, Rozenman Y, Lotan C, Admon D, Raz I, Gotsman MS: Diffuse narrowing of coronary arteries in diabetic patients. *Cardiology* 89:103–110, 1998
14. Henry P, Makowski S, Richard P, Beverelli F, Casanova S, Louali A, Boughalem K, Battaglia S, Guize L, Guermonprez JL: Increased incidence of moderate stenosis among patients with diabetes: substrate for myocardial infarction? *Am Heart J* 134: 1037–1043, 1997
15. Ueda Y, Asakura M, Yamaguchi O, Hirayama A, Hori M, Kodama K: The healing process of infarct-related plaques: insights from 18 months of serial angioscopic follow-up. *J Am Coll Cardiol* 38:1916–1922, 2001
16. Beckman JA, Creager MA, Libby P: Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA* 287:2570–2581, 2002
17. Vague D, Raccah D, Juhan-Vague I: Hemobiology, vascular disease and diabetes with special reference to impaired fibrinolysis. *Metabolism* 41:2–6, 1992
18. Davi G, Catalano I, Averna M, Notarbartolo A, Strano A, Ciabattoni G, Patrono C: Thromboxane biosynthesis and platelet function in type II diabetes mellitus. *N Engl J Med* 322:1769–1774, 1990
19. Sagel J, Colwell JA, Crook L, Laimins M: Increased platelet aggregation in early diabetes mellitus. *Ann Intern Med* 82:733–738, 1975
20. Yokoyama I, Momomura S, Ohtake T, Yonekura K, Nishikawa J, Sasaki Y, Omata M: Reduced myocardial flow reserve in non-insulin dependent diabetes mellitus. *J Am Coll Cardiol* 30:1472–1477, 1997
21. Nahser PJ Jr, Brown RE, Oskarsson H, Winniford MD, Rossen JD: Maximal coronary flow reserve and metabolic coronary vasodilation in patients with diabetes mellitus. *Circulation* 91:635–640, 1995
22. McDonagh PF, Hokama JY, Copeland JG, Reynolds JM: The blood contribution to early myocardial reperfusion injury is amplified in diabetes. *Diabetes* 46:1859–1867, 1997
23. Oliver MF, Opie LH: Effects of glucose and fatty acids on myocardial ischemia and arrhythmias. *Lancet* 343:155–158, 1994
24. Sun D, Nguyen N, DeGrado TR, Schwaiger M, Brosius FC 3rd: Ischemia induces translocation of the insulin-responsive glucose transporter GLUT4 of the plasma membrane of cardiac myocytes. *Circulation* 89:793–798, 1994
25. Malmberg K, Ryden L, Efendic S, Herlitz J, Nicol P, Waldenstrom A, Wedel H, Welin L: Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol* 26:57–65, 1995