Diabetes Mellitus: A Cardiologist's Perspective

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Research Interests: The focus of my research is cardiac metabolism and mechanical function in transgenic models of altered myocardial energetics. Metabolic and mechanical measurements are made in isolated perfused organs and the intact animal using standard biochemical methods, 23-Na, 39-K, 31-P and 13-C NMR spectroscopy, MR imaging and transthoracic echocardiography. My clinical interest is cardiovascular disease in women.

Introduction

Diabetes is associated with an increased risk of coronary artery disease (CAD) and increased cardiovascular mortality. Figure 1 shows the cumulative mortality due to CAD in male and female patients with insulin-dependent diabetes mellitus (IDDM) diagnosed before the age of 21 (1, 2). Between the ages of 30 and 55 years, CAD mortality was 35%. This contrasts with non-diabetic men and women from the Framingham cohort who experienced 8% and 4% mortality respectively (3). Increased mortality due to CAD is also increased in patients with non-insulin dependent diabetes mellitus (NIDDM). Figure 2 shows age-adjusted CAD mortality rates in men and women during the 24 years following diagnosis of NIDDM and for non-diabetic men and women in the Framingham cohort (2, 4). Higher CAD mortality includes sudden cardiac death and deaths from pump either of which can occur in the setting of myocardial infarction (MI). The goal of this review is to discuss MI in patients with diabetes mellitus including prognosis, acute treatment, secondary prevention strategies and revascularization.

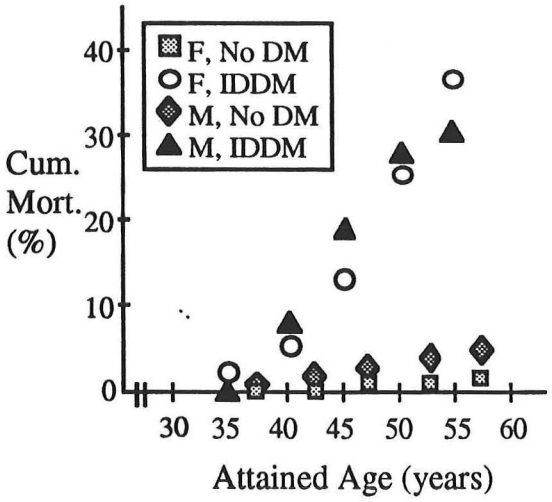

Figure 1. Cumulative CAD mortality in men and women with and without IDDM (adapted from (2)).

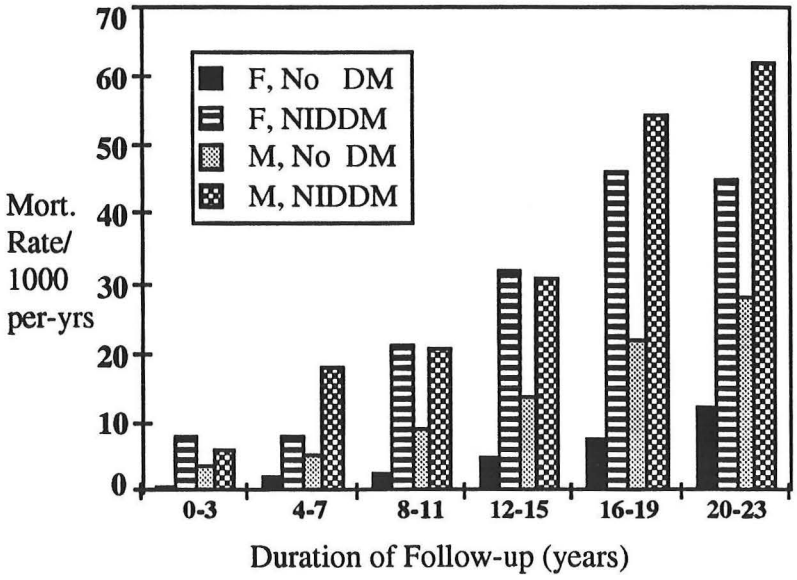

Figure 2. CAD mortality rate per 1000 person years in men and women with and without NIDDM (adapted from (2)).

Prognosis ater Myocardial Infarction

In the pre-thrombolytic era, diabetic patients had a poor immediate and long term prognosis after MI. In 34 year follow-up in the Framingham Study, the relative risk of fatal CHD was 1.8 (95% CI 1.2-2.9) in men and 2.6 (95% CI 1.4-4.7) in women and the risk of recurrent MI was twice as high in women as men (5). In the Minnesota Heart Survey, diabetic individuals had an odds ratio of in-hospital death after MI 1.5 times that of non-diabetic patients. Among those who survived to be discharges from the hospital, the risk of death was 40% higher in diabetic patients compared to non-diabetic patients (6). The National Hospital Discharge Survey diabetes increased in hospital mortality with acute MI in younger age-groups, particularly among men (7).

Abbud *et al.* reported the New Jersey experience using the statewide Myocardial Infarction Data Acquisition System (MIDAS) which describes 42,595 patients (22.8% with diabetes) with MI discharged from 90 nonfederal hospitals in 1986 and 1987 (8). Diabetes was more prevalent among female, black and older patients. Both in-hospital and 3 year mortality rates were higher for patients with diabetes (21.5% versus 19.2% and 46.7% versus 37.8%, respectively, $p<0.001$). Diabetes was an independent predictor of mortality even after adjustments were made for a number of clinical confounders. The relative risk of death from MI, shown in Table 1, was greatest for diabetic patients in the youngest age groups.

Table 1. Relative Risk of Death after MI in Diabetic Patients According to Age

Age	Relative Risk of Death
30-49 years	1.87 (1.45-2.42)
50-69 years	1.36 (1.28-1.46)
70-89 years	1.17 (1.11-1.23)

95% CI in parentheses.From (8)

Behar *et al.* reported the impact of diabetes on ten year survival after acute MI in patients enrolled in the Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT). The prevalence of treated diabetes in the SPRINT registry was 11% (624 of 5708 patients). The 10 year relative risk of death (adjusted for age, previous MI, previous angina, hypertension, congestive heart failure (CHF), markers of infarct size and arrhythmias) is shown in Table 2. (9). In this study, patients with IDDM have a higher relative risk of death following MI compared to patients with NIDDM.

Table 2. Adjusted Relative Risk of Death in Diabetic Subgroups from the SPRINT Registry

Subgroup	Relative Risk of Death
NIDDM men	1.32 (1.10-1.58)
IDDM men	1.75 (1.26-2.45)
NIDDM women	1.41 (1.10-1.82)
IDDM women	2.59 (1.89- 3.56)

95% CI in parentheses. From (9).

Six major trials (of at least 1000 patients) of thrombolytic therapy versus placebo reported data on diabetic patients: the second International Study of Infarct Survival (ISIS-2) (10), ISIS-3 (11), the Intravenous Streptokinase in Acute Myocardial Infarction study (ISAM)

(12), the Estudio Multicentrico Estreproquinesa Republicas de America del Sur trial (EMERAS) (13), the Anglo-Scandinavian Study of Early Thrombolysis (ASSET) (14) and the Late Assessment of Thrombolytic Efficacy study (LATE) (15). A meta-analysis of early mortality and morbidity results from these trials has been performed by the Fibrinolytic Therapy Trialists' (FTT) Collaborative Group(16). Over 43,000 patients were randomized in these six trials and about 10% had diabetes. Five week mortality in non-diabetic patients receiving thrombolysis was significantly lower than in controls (8.7% versus 10.2%). Five week mortality in diabetic patients receiving thrombolysis was also significantly lower than in controls (13.6% versus 17.3%). In either the treatment or control arm, diabetic patients had higher 5 week mortality than non-diabetic patients.

In the thrombolytic era, patients with IDDM still have a higher relative risk of death following MI compared to patients with NIDDM (17-20). Pooled 30 day mortality shows that IDDM patients have a 1.3 relative risk of death following acute MI compared to patients with NIDDM (18).

Thus, in both the pre-thrombolytic and thrombolytic eras, diabetic patients have a poorer prognosis following MI compared to non-diabetic patients. There are a number of different factors which might account for this poor prognosis in diabetic patients:

- a higher burden of cardiac risk factors;
- more frequent silent MI which is undiagnosed and therefore untreated;
- larger infarct size and greater residual ischemic burden
- under-utilization of standard therapies shown to decrease mortality;
- standard therapies less efficacious or
- the presence of diabetes in an independent risk factor for mortality following MI.

Cardiac Risk Factors in Diabetics with Acute MI

Diabetic patients may have a poorer prognosis following MI simply because they have a higher burden of standard cardiac risk factors including increasing age, hypertension, smoking and hypercholesterolemia. Table 3 shows the mean age and prevalence of selected cardiac risk factors in diabetic and non-diabetic patients with acute MI in five large trials. From these pooled data, diabetic patients are more likely to be a few years older with hypertension and hypercholesterolemia and are less likely to have smoked.

Table 3. Prevalence of Selected Cardiac Risk Factors in Diabetic and Non-diabetic Patients with Acute MI

	Age (yrs.)		Smok. (%)		Htn. (%)		HChol. (%)	
Reference	D	ND	D	ND	D	ND	D	ND
WMONICA (n=5,322) (21)	62	58	33	42	61	48	33	31
TAMI (n-=1071) (20)	59	56	64	80	64	40	22	14
GUSTO-1 (n=40,832) (18)	64	61	61	71	54	35	55	34
ISG Trial (n=8,055) (17)	64	62	58	73	45	30	24	18
GISSI-2 (n=11,667) (19)	NA	NA	58	57	31	24	27	22
pooled			55	65	51	35	32	24

D = diabetic; ND = non-diabetic; Htn. = hypertension; HChol. = hypercholesterolemia

In all five of these studies, diabetic patients had a worse prognosis than non-diabetic patients following acute MI but in only one study are the relative risk estimates adjusted for

differences risk factors. Thus, it is difficult to assess if the increased burden of traditional CAD risk factors is solely responsible for the poorer prognosis following myocardial infarction. Yudkin compared the theoretical benefits of coronary risk factor reduction in non-diabetic and diabetic patients using detailed observations of cause specific 10 year mortality from 342,815 non-diabetic and 5,163 diabetic men screened for the Multiple Risk Factor Intervention Trial (MRFIT) (22). He then estimated the effects of different risk factor modifications on CAD mortality in 1000 non-diabetic and 1000 diabetic men aged 35-57 without myocardial infarction which is shown in Table 4.

Table 4. Reductions in CAD Death Due to Modification of Selected CAD Risk Factors in Non-diabetic and Diabetic Men.

	Non-diabetic men	Diabetic Men
CAD Deaths/1000 w/o Tx	14.4	54.2
Reductions in death with:		
Tx SBP > 142 mmHg	0.58	3.03
Tx chol > 6.3 mmol/L	0.82	2.59
Stop smoking	2.74	7.88

Tx = treatment; from (22).

Given that this data is generated in men without MI and that treating a cardiac risk factor may reduce its impact on CAD mortality it does not eliminate it, it would appear that reductions in death from treatment of hypertension and hypercholesterolemia as well as cigarette cessation does not equalize total CAD deaths in non-diabetic and diabetic men. This suggests that other variables may play a role in the poorer prognosis of diabetic patients. Yudkin suggests in fact that standard risk factors contribute minimally to the raised cardiovascular risk. Instead, he suggests that three new risk factors may contribute to excess cardiovascular risk in diabetics: elevated plasminogen activator inhibitor, elevated pro-insulin-like molecules and microalbuminuria (23).

Microalbuminemia, the excretion of small quantities of albumin into the urine, is a predictor of increased risk of diabetic nephropathy (24). It is also a risk marker for cardiovascular disease in patients with NIDDM and IDDM (25-28). Microalbuminuria is also a risk marker for CAD in patients without diabetes (29). Yudkin *et al.* reported increased odds ratio for the development of coronary heart disease in patients independent of the presence of diabetes or hypertension(30). The risk factor adjusted odds ratio for the development of coronary heart disease (CHD) in patients with microalbuminuria are shown in Table 5.

Table 5. Odds ratio for the development of CHD with Microalbuminuria

Adjustment	Odds Ratio (95% CI)
Unadjusted	5.70 (1.95-16.7)
Adjusted for multiple risk factors	6.38 (1.91-21.4)
Adjusted, w/o diabetic subjects	8.91 (2.39-33.2)
Adjusted, w/o hypertensive subjects	9.54 (1.86-48.9)

From (30)

Microalbuminuria may be a manifestation of a generalized vasculopathy with endothelial damage contributing to atherosclerotic and thrombotic processes (23). Whether this represents an important risk factor for mortality in diabetic compared to nondiabetic patients presenting with acute MI is uncertain.

Elevated blood glucose has been associated with poor prognosis in diabetic patients with acute MI (31) and elevated glycosylated hemoglobin levels have been associated with higher cardiovascular mortality and the prevalence of CAD (26, 32). However, a benefit of intensive insulin treatment for glycemic control on reduction of cardiovascular deaths or myocardial infarction has not been established (33) (34, 35)

The Diabetes Insulin-Glucose in Acute Myocardial Infarction (DIGAMI) study demonstrated that insulin-glucose infusion followed by multidose insulin treatment reduces one year mortality in diabetic patients with acute MI particularly among non-insulin dependent diabetic patients without previous insulin treatment (36). Over 1 year, mortality was 26% in the control group versus 19% in the insulin treated group ($p<0.05$). During one year of follow up, 18% of patients in both groups suffered reinfarctions, but 45% of the reinfarctions were fatal in the control group versus 28% in the insulin treated group although this did not reach statistical significance (36). This suggests that hyperglycemia may be associated with at least poorer long term prognosis following myocardial infarction.

Silent Infarction

The idea that diabetic patients with CAD are more likely to have painless myocardial ischemia and infarction was born over 35 years ago, when Bradley and Schonfeld reported that chest pain was either mild or absent in 100 each diabetic and non-diabetic patients admitted with a proven with myocardial infarction from 1958 to 1961 (37). Table 6 shows the percentage of non-diabetics and diabetic patients who presented with certain sets of symptomatology. It is important to note that while only a modest majority of diabetic patients had classical chest pain, over one third had symptoms such as dyspnea, vomiting or fatigue which led their physician to suspect MI. Thus, only in 5% of diabetic patients was myocardial infarction actually "silent" while is was "painless" in 42%.

Table 6. Symptoms in Non-diabetic and Diabetic patients with Proven MI

Symptoms	Non-diabetics	Diabetics
Very severe or severe pain	76%	27%
Moderate or light pain	17%	30%
No pain, other symptoms	6%	37%
No pain, no symptoms	0%	5%
Undetermined	1%	1%

From (37).

In 61 patients in whom a healed transmural MI was found at autopsy, diabetes was more prevalent in those 28 patients with a clinically unrecognized history of MI than those 33 patients with a clinically recognized MI (43% vs 15%) (38). From the Framingham study, truly silent MI, as documented by biennial ECGs, occurs in 12% of patients and is more common in diabetic patients (39).

Infarction Size and Severity of CAD

Poorer prognosis of acute MI in diabetic patients does not appear to be explained by a larger infarct size as reflected by peak serum CK levels. In a number of studies in the pre-thrombolytic and thrombolytic era, diabetic patients have smaller peak CK values than non-diabetic patients despite increased mortality from acute MI (40-42). In contrast, diabetic patients with acute MI are more likely to anterior infarction (18, 19, 42, 43) and multivessel coronary artery disease (18, 20, 44)

Treatment of Myocardial Infarction

Currently, standard therapy for all patients admitted to the CCU with MI within 12 hours of symptom onset includes thrombolytic therapy or primary angioplasty, aspirin, β-blockers and ACE inhibitors (45). Are these therapies as efficacious and as frequently prescribed in diabetics compared to non-diabetics? Could this account for differences in prognosis following MI?

Thrombolytic Therapy. Thrombolytic therapy is the standard of care for treatment of MI (45). In an overview of nine trials (enrolling more than 1000 patients each) of thrombolytic therapy versus placebo, The Fibrinolytic Therapy Trialists' Collaborative Group reported an 18% reduction in 35 day mortality in 29,315 patients allocated to receive thrombolytic therapy (16).

Thrombolysis appears to be as affective in diabetic patients as in non-diabetic patients at least acutely in terms of artery patency, reocclusion rates and relative reductions in mortality. In the GUSTO Angiographic study, 2,431 patients were assigned to 90 minute post-thrombolysis angiography to assess infarct artery patency rates and left ventricular function (46). Ninety-minute patency rates, reocclusion rates and ejection fraction were similar in diabetic and non-diabetic patients. In this subgroup, both adjusted and unadjusted 30 day mortality were higher in diabetic versus non-diabetic patients as was found in the study overall. Granger *et al.* evaluated the angiographic characteristics of 148 diabetics and 923 non-diabetics enrolled in a number of the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) trials (20). Angiographic patency rates at 90 minutes were similar in patients with and without diabetes (71% vs 70%, respectively) and there were no differences in reocclusion rates. However, diabetics had nearly twice the in-hospital mortality rate (11% vs 6%, $p < 0.02$).

In the meta-analysis of early mortality thrombolytic therapy in six trials detailing the outcome of diabetics, the relative reduction in 35 day mortality was as good if not better in diabetic patients receiving thrombolytic therapy compared to non-diabetic patients (21% vs 15%, respectively); furthermore, there was no excess in bleeding or hemorrhagic stroke in diabetic patients (16). Lynch *et al.* evaluated in-hospital mortality and morbidity in diabetic and non-diabetic patients admitted during two time periods: from 1984-1987 (pre-thrombolytic) and from 1990-1992 (47). Following the introduction of thrombolytic therapy, there was a reduction in mortality among non-diabetic patients from 17% to 8.5% (49% reduction) and among diabetics from 30% to 17% (42% reduction). Thrombolytic therapy appears to be an effective therapy in diabetics patients. Are diabetic patients less likely to receive this effective therapy compared to non-diabetic patients because of specific contraindications to use of thrombolytic therapy in diabetic patients?

Although, diabetic retinopathy has been classified as an absolute contraindication to thrombolytic therapy in patients with acute MI because of the risk of retinal hemorrhage

(48), few of the large thrombolytic trials included diabetic retinopathy among exclusion criteria. Moreover, there is no clear evidence that patients with diabetic retinopathy are at risk for intraocular hemorrhage following thrombolytic therapy. There is one case report, of which I am aware, of retinal hemorrhage after thrombolytic therapy in a 46 year old diabetic man with no permanent loss of vision (49). In the GUSTO-I Trial, 12 patients had an ocular hemorrhage (0.03%), in which 11 were extraocular and 1 was intraocular (in a non-diabetic patient); in the 6,011 diabetic patients, only one had an ocular hemorrhage which was an eyelid hematoma secondary to a documented fall (50). In 148 diabetic and 923 non-diabetic patients enrolled in the TAMI trials, no retinal hemorrhages were observed (20).

Are there other contraindications or selection biases which exclude diabetic patients preferentially from treatment with thrombolytic therapy? Fava *et al.* evaluated 898 patients admitted with acute MI and found that 32% of diabetic patients received thrombolytic therapy compared to 44% of non-diabetic patients ($p<0.001$) (31). Pfeffer *et al.* compared the clinical features of patients who had or had not received thrombolytic therapy who were enrolled in the Survival and Ventricular Enlargement (SAVE) Study from 1987 to 1990 (51). Randomization to the SAVE study occurred between 3 and 16 days after acute MI in patients with an ejection fraction less than 40%. Of the 2231 patients randomized, 33% received thrombolytic therapy. Patient demographics indicated that patients at higher risk for adverse outcome at the time of acute MI were less likely to receive thrombolytic therapy. Table 7 shows the odds ratio of receiving thrombolytic therapy for specific subgroups of patients.

Table 7. Odds ratio of receiving thrombolysis in Patient Subgroups

Variable	Odds Ratio (95% CI)
Widowed	0.77 (0.49-1.27)
Hypertension	1.06 (.087-1.31)
Pior MI	0.68 (0.68-0.87)
Diabetes	0.67 (0.52-0.87)
Neurological diseases	0.63 (.046-0.86)
Employed	1.33 (1.06-1.68)

From (51)

The reasons for reduced utilization of thrombolysis in diabetic patients during this study period is not clear. It may be that physicians broadly consider diabetic patients as generally less healthy and therefore exclude them under the broad exclusion criteria for patients with serious disease. In the ISAM trial, patient were excluded if they had, among others, "any severe disease that would exclude the patient in the opinion of the clinical investigator" (12). In the ASSET study, diabetic retinopathy was an exclusion criteria as was "any other serious organic" disease (14). In ISIS-3, contraindications were at the discretion of the responsible physician. It was suggested that contraindications may include, among others, "conditions associated with only a small likelihood of worthwhile benefit (such as... high risk of death from some other life-threatening disease)" (11). In the more recent GUSTO-I trial which compared different strategies of thrombolysis in acute MI, exclusion criteria were essentially limited to previous stroke, active bleeding, recent trauma or major surgery and severe uncontrolled hypertension (52).

Given the poor prognosis of diabetics following acute MI and the clear benefit:risk ratio of treatment which has been well described in recent literature, maximum utilization of thrombolysis in this subgroup will hopefully be realized.

Beta-blockers. It has been suggested that the use of beta-blockers in diabetic patients is contraindicated because beta-blockers will potentiate insulin-induced hypoglycemia and blunt the physiological response to hypoglycemia. This concern was voiced over thirty years ago when the use of the nonselective beta-blocker propranolol was found to delay the recovery of blood glucose following hypoglycemia and prevented its associated tachycardia (53). However, these effects are less pronounced or, in most studies, absent with cardioselective beta-blockers such as metoprolol (54-57).

Because of these perceived side effects, are beta-blockers are used less often in diabetic patients than non-diabetic patients than non-diabetics? Few studies address this question. In a study of unstable angina, 32% of diabetic patients and 46% of non-diabetic patients were treated with beta blockers ($p<0.008$) (58). In the Scandinavian Simvastatin Survival Study (4S), in 4,444 patients with coronary heart disease (approximately 80% with infarction), the use of beta-blockers was not different in diabetic and non-diabetic patients (61% versus 57%, respectively) (59). In the GUSTO-1 Angiographic Substudy, the use of beta-blockers as adjunctive therapy to thrombolysis (in about 46% of patients) and upon discharge (in about 62% of patients) was similar in diabetic and non-diabetic patients (46).

A number of randomized trials both in the pre-thrombolytic and thrombolytic eras have shown that acute and chronic administration of beta-blocker to patients admitted with suspected MI reduces mortality, reinfarction and sudden cardiac death, particularly in high risk patients (reviewed in (48). Diabetic patients, in particular, benefit from beta-blocker use as well. Table 9 reveals mortality data from both acute and chronic use trials which compared beta-blocker versus placebo in diabetic and non-diabetic patients admitted with suspected acute MI. These studies are a heterogeneous mix with a number of variables including type of beta-blocker used (timolol, propranolol, pindolol, metoprolol, atenolol), timing of initiation of therapy, (from immediate injection to 21 days after symptom onset) duration of follow-up (15 days to 3 months in the acute use group and 12-48 months in the chronic use group) and number of diabetic patients enrolled (36 to 958). When the clinical features of the diabetic population were described, approximately half of the diabetic patients were treated with diet alone, less than 20% were treated with insulin and the remainder were treated with oral hypoglycemics (59,62).

This table illustrates several important features. In both the placebo and treatment groups, diabetic patients had higher unadjusted mortality than non-diabetic patients. With the exception of a single study, either acute or chronic treatment with beta-blockers reduced mortality in the diabetic patients to a greater extent than in non-diabetic patients.

In only one study, diabetics had increased mortality from beta-blocker treatment: the Australian and Swedish Pindolol Study Group (60). Patients were enrolled in this study from 1978 to 1980 if they had myocardial infarction and electrical and/or mechanical complications and treatment was started 1-21 days after infarction. No clinical description is provided of the diabetic group although it is clearly small with 5 deaths in the placebo group and 6 deaths in the treatment group. In summary then, there are no clear "glycemia" related contraindications to the use of cardioselective beta-blockers in diabetic patients and there are clearly benefits to their use acutely and chronically following acute MI.

Table 8. The Effect of Beta-blocker Use on Mortality in Diabetic and Non-diabetic Patients after Acute MI.

Reference	Placebo		β-blocker		Δ with Tx	
Acute Use	Diabetic	Non-diabetic	Diabetic	Non-diabetic	Diab.	NonD.
MIAMI (61)	25/221 (11.3)	117/2680 (4.4)	11/192 (5.7)	112/2685 (4.2)	-50%	-5%
Goteborg (62)	12/67 (17.9)	50/630 (7.9)	4/53 (7.5)	36/645 (5.6)	-58%	-29%
ISIS-I (63)	40/495 (8.1)	321/7495 (4.2)	30/463 (6.5)	281/7574 (3.7)	-22%	-12%
pooled data	77/783 (9.8)	488/10805 (4.5)	44/708 (6.2)	429/10904 (3.9)	-37%	-13%
Chronic Use						
Timolol (57)	14/46 (30.5)	138/893(15.5)	6/53 (11.3)	92/892 (10.3)	-63%	-34%
BHAT (64)	33/229 (14.4)	155/1692 (9.2)	22/236 (9.3)	116/1680 (6.9)	-35%	-25%
(60) Pindolol	5/22 (22.7)	42/244 (17.2)	6/14 (42.9)	39/249 (15.7)	+189%	-9%
Kjekshus(64)	33/141 (23.4)	103/806 (12.8)	13/127 (10.2)	42/642 (6.5)	-56%	-49%
pooled data	85/438 (19.4)	438/3635 (12.0)	47/430 (10.9)	289/3463 (8.3)	-44%	-31%

Δ = change; Tx = treatment; Diab. = diabetic; NonD. = non-diabetic; percentages noted in parentheses. Adapted from (64).

Aspirin Use. In its scientific statement regarding aspirin as a therapeutic agent in cardiovascular disease, the American Heart Association recommends aspirin should be administered routinely to virtually all patients with acute MI (65). The benefits of aspirin in the setting of acute MI were clearly demonstrated inISIS-2 (10). Over 17,000 patients who were admitted to 417 hospitals within 24 hours of the onset of symptoms of acute MI were randomized in a 2 X 2 factorial design depicted in Figure 3. Half of all patients received 1.5 mU of intravenous streptokinase and half received a placebo infusion. Half of all patients received 160 mg of aspirin chewed immediately and then daily for one month or placebo tablets.

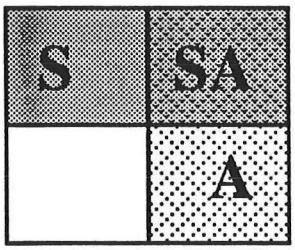

Figure 3. 4 X 4 Factorial Design for Streptokinase (S) and Aspirin (A) randomization in ISIS-2(10).

Table 9. 35 Day Vascular Mortality According to Treatment Allocation in All Patients

Treatment	Vascular Deaths
All streptokinase	791/8592 (9.2%)
All aspirin	804/8587 (9.4%)
Both	343/4292 (8.0%)
Neither	568/4300 (13.2%)

From (10).

Table 9 shows 35 day vascular mortality in patients according to treatment allocation. In the aspirin group, there was significant reduction in non-fatal MI and non-fatal stroke and there was no increase in cerebral hemorrhage or in major bleeding that required transfusions. Thus aspirin has a favorable benefit to risk ratio as a proven therapy of MI.

Approximately 7.5% of the patients enrolled in ISIS-2 were diabetics. Table 10 shows 35 day vascular mortality in diabetic and non-diabetic study participants according to treatment. Data in this table illustrates several important points. First, streptokinase reduces mortality in all patients compared with placebo with a greater relative reduction in mortality

in diabetic patients. Unlike in non-diabetic patients, there is no mortality benefit with the use of aspirin in diabetic patients nor does the benefit for combination therapy reach statistical significance.

Table 10. Thirty-Five Day Vascular Mortality According to Treatment Allocation in Diabetic and Non-diabetic Patients

	All SK	All SK-P	All ASA	All ASA-P	SK/ ASA	SK-P /ASA-P
Diabetic	73/619 (11.8)*	115/668 (17.2)	94/645 (14.6)	94/642 (14.6)	40/306 (13.1)	61/329 (18.5)
Nondiab	704/7871 (8.9)*	900/7823 (11.5)	701/784 7 (8.9)*	903/7847 (11.5)	298/3933 (7.6)*	497/3909 (12.7)

*Treatment better than placebo based on odds ratio and 95% CI. Percentages in parentheses; SK=streptokinase; SK-P=placebo infusion; ASA=aspirin; ASA-P=placebo. From(10).

In a trial as large as ISIS-2, reliable identification of patient subgroups in whom treatment is effective or ineffective is not always possible. False negative results in some subgroups may occur due to type 2 error or as a consequence of multiple comparisons (66). To illustrate this, the ISIS-2 investigators subdivided patients with respect to their astrological birth signs. Table 11 shows 35 day vascular mortality (percentage) in Gemini or Libras compared to other astrological signs. It would appear that patients born under these two signs did not benefit from aspirin or combination therapy while patients born under all other signs benefited greatly from treatment in all groups.

Table 11. Thirty-Five Day Vascular Mortality According to Treatment Allocation in Diabetic and Non-diabetic Patients

Zodiac	All SK	All SK-P	All ASA	All ASA-P	SK/ ASA	SK-P /ASA-P
Gem/Lib	9.2 *	12.1	11.1	10.2	9.1	11.2
All others	9.2 *	11.9	9.0 *	12.1	7.8 *	13.6

*Treatment better than placebo based on odds ratio and 95% CI. SK=streptokinase; SK-P = placebo infusion; ASA=aspirin; ASA-P=placebo tablet. From(10).

Thus, it is likely that the lack of benefit in diabetic patients of aspirin in acute MI in this study is a false negative result. Is there any other data which supports the use of aspirin during acute MI in this patient subgroup? The Antiplatelet Trialists' Collaboration reviewed over 150 trials of antiplatelet therapy with results available before March 1990 (67). Patients were subdivided into high and low risk. Four high risk categories were acute MI, previous MI, previous stroke or TIA and other relevant vascular history (CAD, PVD, USA etc.). In 29 trials of these high risk patients, separate information was available regarding age, gender, blood pressure and the presence of diabetes. Absolute effects of antiplatelet therapy on vascular events (non-fatal MI, nonfatal stoke and vascular death) in diabetics and non-diabetic patients are shown in Table 12.

Table 12. Vascular Events in Diabetics and Non-diabetic Patients in 29 Trials of High Risk Patients Randomized to Placebo or Antiplatelet Therapy

Diabetes	Antiplatelet Rx	Placebo	% reduction
No	2700/21136 (12.8)	3466/5308 (16.4)	22%
Yes	415/2248 (18.5)	502/2254 (22.3)	17%

Percentage in parentheses. Adapted from (67).

Is the presence of diabetic retinopathy a contraindication to aspirin use? This question was answered in a multicenter randomized clinical trial sponsored by the National Eye Institute called the Early Treatment Diabetic Retinopathy Study which was (68, 69). In one portion of the study, 3711 diabetic patients were treated with aspirin (650 mg/day) or placebo and followed for an average of 5 years for the occurrence of diabetic ocular events. While aspirin did not prevent the development of high risk proliferative retinopathy nor reduce the risk of vision loss, it did not increase the risk of vitreous hemorrhage.

ACE inhibitors. For patients within the first 24 hours of suspected acute MI with anterior ST segment elevation or with clinical heart failure or an ejection fraction less than 40%, treatment with ACE inhibitors is recommended (45). Krumholz *et al.* evaluated the use of ACE inhibitors in 1,228 elderly patients discharged following acute MI with ejection fractions less than or equal to 40% and no contraindications to ACE inhibitors (45). In a multivariate analysis, an increased prescribed use of ACE inhibitors at discharge was correlated with the presence of diabetes mellitus, congestive heart failure and ventricular fibrillation. In a retrospective analysis of the GISSI-3 study, Zuanetti *et al.* reported that treatment of diabetic patients within 24 hours of suspected MI with lisinopril reduced 6 week mortality by approximately 40% and this was significantly greater than the effect in non-diabetic patients; moreover, this survival benefit in diabetic patients persisted at 6 months (70).

Revascularization

While revascularization is not a standard therapy for acute myocardial infarction, it is often performed during long term follow-up and thus can influence determinations of prognosis. Therefore, should one revascularization strategy have increased mortality in a patient subgroup such as diabetes, it's adverse consequences might contribute substantially to overall estimates of mortality. For example, in the TIMI II trial, patients with acute MI were treated with intravenous tPA and then were randomly assigned to either the invasive strategy or the conservation strategy. Those in the invasive strategy underwent coronary angiography within 18 to 48 hours of randomization with percutaneous transluminal coronary angioplasty (PTCA) of the infarct artery when the anatomy was appropriate. Coronary artery bypass grafting (CABG) was recommended when coronary anatomy was not suitable for PTCA. In a subgroups analysis, multiple logistic regression analyses for selected combinations of variables, including the presence or absence of diabetes and the use of invasive or conservation strategy, was performed (44). Table 13 lists the relative risk of death at 42 days or earlier for these regression analyses. There was a marked increase in mortality in diabetic patients randomized to the invasive strategy in which two-thirds of these patients underwent PTCA or CABG. The relative use of CABG vs PTCA was not reported.

Table 13. RR for Death in TIMI II Subgroups

Variables	RR (99% CI)
No prior AMI, no D, CS	1.0
No prior AMI, no D, IS	1.2 (0.7-2.1)
No prior AMI, D, CS	1.2 (0.4-3.5)
No prior AMI, D, IS	4.3 (2.0-9.0)

AMI=acute MI; D=diabetes; CS =conservative strategy; IS=invasive strategy; RR=relative risk; From (44).

The Bypass Angioplasty Revascularization Investigations (BARI) Trial was published in July 1996 (34). Patients with multivessel disease were recruited between 1988-1991 and were randomly assigned to an initial treatment strategy of CABG (N=914) or PTCA (n= 915) and were followed for an average of 5.4 years. Patients had an average of 3.5 clinically important lesions, 41% had triple vessel disease and mean LVEF was 57%. Half the patients had a history of myocardial infarction although only 18% had Q waves on the EKG, 20% had medically treated diabetes and 98% had angina within the preceding 6 weeks. Clinical outcomes measured were overall mortality, Q wave infarction and stroke. For all patients, Table 14 shows clinical outcomes for all patients in the BARI Trial.

Table 14. Clinical Outcomes for Patients in the BARI Trial

Event	CABG	PTCA
In-hospital mortality	1.3 %	1.1 %
In-hospital QWMI	4.6 %	2.1 % *
In-hospital stroke	0.8 %	0.2 %
5 year survival	89.3 %	86.3 %
Any revasc over 5 years	8 %	54 %
CABG	1 %	31 %

p <0.01; from (35).

Diabetic patients were not pre-specified as a population subgroup in the BARI trial. However, in 1992, after enrollment was completed, the safety and data monitoring board requested that diabetic patients be monitored because of concern aroused by the findings of the TIMI II trial discussed above. (44). While the in-hospital mortality rates for the PTCA and CABG were similar among treated diabetics (0.6% vs 1.2%, p=ns), the five year survival for the CABG group was much higher than for the PTCA group (80.6% vs 65.5%, respectively, p=0.003) (Table 15).

Table 15. Clinical Outcomes for all Patients and Diabetic Patients in the BARI Trial

Event	All Patients		Diabetic Patients	
	CABG	PTCA	CABG	PTCA
In-hospital mortality	1.3 %	1.1 %	1.2 %	0.6 %
5 year survival	89.3 %	86.3 %	80.6 %	65.5 % *

*p<=0.003; from (35)

The NHLBI published a clinical alert following this amended subgroup analysis which concluded that "BARI's results indicate that CABG should be the preferred treatment for patients with diabetes on drug or insulin therapy who have multivessel coronary artery disease and need a first coronary revascularization" (71).

Subsequent analysis of the diabetic patients in the BARI trial has been published (34). Diabetic patients were more likely to be modestly older, female, with triple vessel disease, CHF, hypertension and modestly reduced EF. In terms of the treatment, diabetic patients had a higher number of significant coronary lesions, distal stenoses and less complete revascularization. Cardiac mortality rates were 20.6% and 5.8% for PTCA and CABG. respectively among patients with diabetes compared with 4.8% and 4.7%, respectively, for BARI patients. The survival benefit of CABG was limited to use of IMA grafts.

Several explanations have been offered to explain the worse outcome with PTCA in diabetic patients. These patients have a greater prevalence of comorbidity including hypertension and CHF. The extent and severity of CAD is greater with more rapid progression of disease and diabetics have an increased risk of MI perhaps due to unfavorable hematological factors or greater plaque instability. Finally, repeat revascularization procedures are more frequently needed in diabetic patients because of incomplete revascularization and restenosis. (72-74).

Have other studies seen this difference in diabetics? Interestingly, treated diabetic patients in the BARI registry who refused randomization were selected for the treatment with PTCA without compromise in survival compared to CABG (75). The 2100 patients in the registry group had similar baseline characteristics but were not randomized for reasons of patient or physician preference. Approximately one third underwent CABG and two thirds had PTCA while less than 5% did not undergo revascularization. Although mortality in the diabetics was twice as high as nondiabetics, there was no significant difference between PTCA and CABG mortality in either group (72).

Gum *et al.* reported the Mid America Heart Institute experience with CABG versus PTCA of 525 treated diabetic patients with a mean follow-up of 55.5 months (76). Table 16 reveals the clinical outcomes in diabetic patients undergoing CABG or PTCA. Multivariate analysis identified age > 70 years, LV EF < 40%, class IV angina and incomplete revascularization, but not the mode of revascularization, as correlates of late mortality. These authors suggest that CABG provides more complete revascularization and is likely necessary to optimize the prognosis for diabetic patients.

Table 16. Clinical Outcomes in Diabetic Patients Undergoing CABG or PTCA

	CABG	PTCA
Complete revascularization	79 %	42 % *
In-hospital mortality	3.2 %	3.2 %
In-hospital MI	3.2 %	3.9 %
1 year survival	88 %	86 %
6 year survival	70 %	63 %

*p<=0.05; from (76).

Barsness *et al.* reported the Duke University Medical Center experience with 3220 patients (24% diabetic) with multivessel undergoing PTCA or CABG (77). In this study, diabetes was strongly associated with a worse long-term prognosis, but this increased mortality was not significantly different between diabetic patients undergoing PTCA and those undergoing CABG. After adjustment for imbalances in baseline characteristics, 5 year survival in diabetic patients undergoing PTCA or CABG was 86% and 89% respectively compared to 92% versus 93% in non-diabetics undergoing PTCA or CABG respectively. Five year mortality covariates included age, comorbidities, ejection fraction, diabetes, CHF severity and CAD severity. Procedural methods, including extent of revascularization and use of internal mammary artery (IMA) conduits, were similar to those of the BARI trial. These authors suggest that diabetes status alone should not determine the choice of revascularization strategy, rather factors such as extent of CAD and technical considerations should be taken into account.

In summary. Diabetic patients have a poorer prognosis following acute MI compared to nondiabetic patients, particularly in diabetic patients treated with insulin and in women. Increased mortality following MI in diabetic patients is likely multifactorial with increased burden of cardiac risk factors, higher incidence of congestive heart failure, greater severity of CAD and metabolic and mechanical abnormalities specific to diabetes. Standard therapies for acute MI such as thrombolytic therapy, aspirin, beta-blockers and ACE inhibitors are of benefit to diabetic and nondiabetic patients alike. The cardiovascular mortality benefits of additional interventions for the treatment of microalbuminuria and hyperglycemia are uncertain. The optimal strategy for revascularization in diabetic patients depends on a number of anatomic and clinical features including a high rate of restenosis and, in some studies, MI following PTCA as well as the importance of IMA grafting in CABG. All of these factors which should be taken into account when choosing a revascularization strategy.

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