Arrhythmias and Mortality After Myocardial Infarction in Diabetic Patients

Relationship to diabetes treatment

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OBJECTIVE — To assess the relationship between clinical course after acute myocardial infarction (AMI) and diabetes treatment.

RESEARCH DESIGN AND METHODS — Retrospective analysis of data from all patients aged 25–64 years admitted to hospitals in Perth, Australia, between 1985 and 1993 with AMI diagnosed according to the *International Classification of Diseases* (9th revision) criteria was conducted. Short- (28-day) and long-term survival and complications in diabetic and nondiabetic patients were compared. For diabetic patients, 28-day survival, dysrhythmias, heart block, and pulmonary edema were treated as outcomes, and factors related to each were assessed using multiple logistic regression. Diabetes treatment was added to the model to assess its significance. Long-term survival was compared by means of a Cox proportional hazards model.

RESULTS — Of 5,715 patients, 745 (12.9%) were diabetic. Mortality at 28 days was 12.0 and 28.1% for nondiabetic and diabetic patients, respectively ($P < 0.001$); there were no significant drug effects in the diabetic group. Ventricular fibrillation in diabetic patients taking glibenclamide (11.8%) was similar to that of nondiabetic patients (11.0%) but was lower than that for those patients taking either gliclazide (18.0%; $0.1 > P > 0.05$) or insulin (22.8%; $P < 0.05$). There were no other treatment-related differences in acute complications. Long-term survival in diabetic patients was reduced in those taking digitalis and/or diuretics but type of diabetes treatment at discharge had no significant association with outcome.

CONCLUSIONS — These results do not suggest that ischemic heart disease should influence the choice of diabetes treatment regimen in general or of sulfonylurea drug in particular.

Diabetes carries an increased risk of ischemic heart disease (IHD), and diabetic patients admitted to coronary care units (CCUs) have a higher case fatality than nondiabetic patients (1). The mechanisms underlying this increased morbidity and mortality are complex (2). Diabetes treatment may influence outcome after acute myocardial infarction (AMI), but there are inconsistencies in published data (1,3–5). Although phenformin (6,7) and the first-generation sulfonylurea tolbutamide (8–11) may be deleterious in the setting of IHD, the analysis and interpretation in these reports are contentious (1,3,12). In recent studies, second-generation sulphonylureas, metformin and insulin, show no consistent effect on outcome (13–15) but whether there is a higher mortality with first- compared with second-generation sulfonylureas is still debated (16). Most clinical studies have not assessed post-discharge deaths, other IHD risk factors, or the effects of newer therapies such as thrombolysis.

Many patients with NIDDM are treated with a sulphonylurea drug, metformin and/or insulin. Their age and the prevalence of other cardiovascular risk factors reinforce the need for studies examining the relationship between diabetes treatment and short- and long-term outcomes from IHD. We have investigated these associations in a large population-based sample of diabetic patients after an AMI that was managed in urban Australian hospitals.

RESEARCH DESIGN AND METHODS

Study population

Data were collected through the community-based Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Project, an international study sponsored by the World Health Organization (17). The MONICA register in Perth, Western Australia, holds information on all local people aged 25–64 years who were identified from hospital discharge diagnoses and death registrations as having had an AMI between 1984 and 1993 inclusive. Any patient with *International Classification of Diseases, Ninth Revision* (*ICD-9*) code of 410.0 to 411.9 (excluding 411.1, unstable angina) was given a stringent MONICA final diagnosis (definite infarction, possible infarction, ischemic cardiac arrest, not myocardial infarction or insufficient data for classification).

Data collection

MONICA data cover preadmission, presentation, inpatient, and early (28-day) post-AMI periods (17). Oral hypoglycemic drugs and/or insulin taken before AMI, in hospital and at discharge, were recorded for diabetic patients from 1985. As MONICA was concerned with usual clinical care and outcome of AMI over a 10-year period, there

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Abbreviations: AMI, acute myocardial infarction; CCU, coronary care unit; CK, creatine kinase; IHD, ischemic heart disease; MONICA, Monitoring of Trends and Determinants in Cardiovascular Disease.

Table 1—*Admission details of nondiabetic and diabetic patients hospitalized with AMI between 1985 and 1993 in Perth, Western Australia*

	Nondiabetic	Diabetic
n	4,970	745
Age (years)	54.4 ± 7.9	56.2 ± 7.2
Sex (% male)†	89.2	67.4
Current smokers (%)†	43.4	29.7
Known hypertension (%)†	39.9	57.3
Previous AMI†	25.8	37.6
Other medications (%)		
Beta-blocker	21.9	23.4
Calcium-channel blocker†	15.5	27.9
ACE inhibitor†	3.5	10.0
Hypolipidemic agent*	4.0	5.9

Data are *n*, means ± SD, or %. *$P < 0.05$; †$P < 0.001$ by χ^2 test.

was no provision for standardized measurement of plasma glucose, glycosylated hemoglobin, serum potassium, or serum lipid levels. Diabetes type was not recorded routinely. Episodes of AMI occurring <28 days apart were counted only once. Those discharged and not on the Western Australian death register were presumed alive at 28 days. The register provided further information on survival for up to 9 years post-AMI. We selected events classified as AMI that occurred between 1985 and 1993 inclusive. In each case, the MONICA diagnosis was either definite infarction (fatal or nonfatal) or possible infarction in cases where the patient died in hospital.

Statistical analysis

Univariate associations between outcome variables and treatments are shown in tabulations. For patients taking oral agents and/or insulin, multivariate logistic regression was used to assess factors associated with 28-day survival as well as ventricular fibrillation or tachycardia, complete heart block, atrial fibrillation, or pulmonary edema within the first 28 days. A Cox proportional hazards model was used to identify factors related to long-term survival of patients alive at 28 days. The SAS computer package (version 6.07; SAS Institute, Cary, NC, 1991) was used for tabulations and χ^2 statistics, and EGRET (version 0.26.6, SERC, Seattle, WA, 1990) for multivariate regression analyses.

RESULTS — During the 9-year study period, 5,715 patients with AMI were admitted to Perth hospitals, of whom 12.9% were diabetic (Table 1). The diabetic patients were less likely to be managed in a CCU (79 vs. 89%), to receive thrombolytic therapy (21 vs. 32%), and to survive 28 days (72% vs. 88%) when compared with nondiabetic patients ($P < 0.001$ in each case). Ventricular and atrial fibrillation, complete heart block, and pulmonary edema occurred more often in the diabetic group ($P < 0.05$), but ventricular tachycardia was observed significantly less often (21 vs. 32%; $P < 0.001$).

Over two thirds (69%) of the diabetic patients had taken oral hypoglycemic drugs or insulin over the 28 days before admission (Table 2). Of the insulin-treated patients, 86% were on insulin alone and, of the remainder, 68% were also on metformin. The treatment subgroups had similar admission characteristics, except that those on insulin were least likely to smoke and those on metformin alone were most likely to be taking an ACE inhibitor. There were no treatment-related differences in complications of AMI and 28-day mortality ($P > 0.05$; data not shown).

Six different multivariate logistic regression analyses were performed using data from 397 patients on known therapy, the dependent variables being short-term survival and five cardiac complications (Table 3). After adjustment for factors associated with these end points (i.e., age, sex, shock or heart failure at presentation, peak serum creatine kinase [CK], infarction site, smoking, thrombolysis, and treatment with digoxin, diuretics, and aspirin), variables indicating diabetes treatment were added to the model. Since glibenclamide, gliclazide, and insulin are not normally prescribed

Table 2—*Admission details of diabetic patients hospitalized with AMI subdivided according to the type of diabetes treatment at presentation*

	Diet alone	Glibenclamide	Gliclazide	Insulin	Metformin alone	Unknown treatment
n	229	110	111	136	40	119
Age (years)	56.4 ± 7.1	56.6 ± 7.2	56.6 ± 7.2	55.0 ± 8.0	55.4 ± 7.2	56.7 ± 6.6
Sex (% male)	74.7	75.5	63.1	63.2	57.5	58.0
Current smokers (%)*	36.2	27.3	35.1	18.4	45.0	21.9
Known hypertension (%)	59.0	60.9	61.3	52.2	70.0	48.7
Other medications (%)						
Beta-blocker	19.2	28.2	22.5	19.1	30.0	23.5
Calcium-channel blocker	21.8	29.1	31.5	33.8	22.5	30.3
ACE inhibitor*	10.5	9.1	13.5	10.3	25.0	0.8
Hypolipidemic agent	5.2	2.7	2.7	8.8	12.5	7.6
Digitalis	10.1	8.2	8.1	6.6	7.5	12.6
Diuretics	26.8	30.0	25.2	33.8	35.0	30.3

Data are *n*, means ± SD, or %. *$P < 0.001$ by χ^2 test. Columns headed glibenclamide, gliclazide, and insulin identify patients taking these drugs either alone or in combination with metformin. Unknown treatment refers to patients taking a drug for diabetes that could not be identified or was not coded.

Table 3—*Multivariate odds ratios and CIs for short-term survival and complications according to diabetes treatment after adjustment for other variables*

	Reference: glibenclamide		Reference: no treatment	
	Gliclazide	Insulin	Metformin in combination	Metformin alone
Short-term survival	0.7 (0.3–1.4)	0.8 (0.4–1.7)	0.7 (0.4–1.5)	0.4 (0.1–1.3)
Ventricular tachycardia	1.2 (0.6–2.3)	1.1 (0.6–2.3)	0.9 (0.4–1.7)	0.8 (0.3–2.2)
Ventricular fibrillation	1.9 (0.8–4.4)	2.8 (1.2–6.3)*	1.3 (0.6–2.8)	1.4 (0.4–4.7)
Atrial fibrillation	0.6 (0.2–1.7)	0.7 (0.3–1.8)	0.2 (0.1–0.7)*	1.1 (0.3–4.0)
Complete heart block	0.4 (0.1–1.4)	1.1 (0.4–2.8)	1.0 (0.4–3.0)	1.5 (0.4–5.0)
Pulmonary edema	0.7 (0.3–1.5)	0.6 (0.3–1.2)	0.9 (0.4–1.9)	0.5 (0.1–1.4)

*$P < 0.05$.

together, we used one variable to indicate which of these were taken, with glibenclamide the reference group for odds ratios. As metformin is often part of combination therapy, we used a second variable to indicate whether metformin was used alone, in combination with other drugs, or not at all, the last being the reference group. Patients taking insulin had a significantly higher incidence of ventricular fibrillation than those on glibenclamide. There was a similar trend in the case of gliclazide that did not reach statistical significance. Those taking metformin in combination with other agents experienced significantly less atrial fibrillation than patients taking metformin alone or not at all.

The Cox proportional hazards model was fitted to long-term survival data for 333 patients alive 28 days after AMI (Table 4). In those with more than one AMI, the first was taken as the index event. Adjusting variables were age, sex, complications, serum CK rise, previous AMI, smoking, and other cardioactive drugs prescribed at discharge. Patients taking digitalis or diuretics had a significantly reduced long-term survival rate compared with those not prescribed these drugs. There was heterogeneity in outcome between different diabetes treatments that did not achieve statistical significance.

CONCLUSIONS — Reports from the University Group Diabetes Program (6,8) began the long-running debate on the effect of diabetes treatment on outcome after AMI (3,4). A randomized, prospective trial would best assess risks and advantages of current regimens (4) but patients would need to be recruited before or at the time of AMI and followed for a prolonged period. Although retrospective studies have limitations, we used the standardized MONICA inpatient record and subsequent mortality data from a relatively large number of diabetic patients, most of whom had NIDDM, to evaluate outcomes after AMI in relation to treatment. The results do not suggest that treatment for diabetes should be influenced by the presence or risk of IHD.

One in eight subjects on the MONICA database was diabetic, a greater proportion than the adult diabetes prevalence in urban Australian communities (3.4%) (19) and among hospital inpatients (10%) (20). These comparisons confirm increased diabetes-associated morbidity, especially owing to IHD. Because the diagnosis of diabetes was self-reported or determined from case records, there are likely to have been undiagnosed patients in the nondiabetic group. However, our aim was to assess differences in outcome between diabetes treatments rather than between patients with and without diabetes, while patients diagnosed in hospital were included in the analysis of long-term survival.

Largely because of MONICA recruitment criteria, there was no significant difference in age between nondiabetic and diabetic patients but, consistent with previous studies (1), our diabetic patients were more likely to be female, hypertensive, dyslipidemic, and nonsmokers and to have worse short-term mortality. Management of diabetic patients differed from that of nondiabetic individuals, with significantly fewer admitted to CCU and given thrombolysis, especially those on insulin. This may have reflected physician attitudes to diabetes and/or a greater prevalence of clinically silent myocardial ischemia in diabetic patients (20). That ventricular tachycardia was observed less often in the diabetic patients may have been due to the fact that fewer were monitored on CCU but this would also mean that the proportions of diabetic patients with other important dysrhythmias were underestimates.

Glibenclamide-treated patients were the least likely to experience ventricular fibrillation, with an incidence similar to that in nondiabetic subjects (11.0%). Compared with those on glibenclamide, insulin-treated patients had a significantly higher incidence of ventricular fibrillation, and there was a similar trend in the case of gliclazide that did not reach statistical significance. Second-generation sulfonylurea drugs block myocardial ATP-dependent potassium (K^+_{ATP}) channels, an action which is antiarrhythmic (21). Consistent with trends found in the present study, glibenclamide reduces ischemia-associated ventricular fibrillation in animal studies (4). K^+_{ATP} channel closure can also interfere with mechanisms that protect the myocardium against ischemia (4). We found no treatment-related differences in short-term mortality despite a reduced tendency to ventricular arrhythmias with glibenclamide, suggesting that the favorable and deleterious effects of second-generation sulphonylureas on K^+_{ATP} channels have no net effect on prognosis after AMI.

Although prolonged, intensive insulin therapy post-AMI reduces mortality at 1 year (22), our results indicate that neither short- nor long-term survival after AMI is related to more conventional diabetes treatments. Thus, although our data and those of others (16,23) suggest that, unlike other therapies for diabetes, second-generation sulphonylureas suppress ventricular arrhythmias, this has limited clinical significance. As the main cause of death among diabetic patients with AMI is pump failure (3), and in the context of other reports (3,4), our results suggest that

Table 4—*Multivariate hazard ratios and CIs obtained from a Cox proportional hazards model for long-term outcome of diabetic patients after discharge from hospital*

Drug	*n*	Hazard ratio (CI)
Digitalis	21	2.6 (1.2–5.6)
Diuretics	111	2.0 (1.1–3.6)
Glibenclamide	103	1.0 (—)
Gliclazide	82	1.6 (0.8–3.2)
Insulin	76	1.1 (0.5–2.4)
Metformin		
In combination	56	0.7 (0.3–1.7)
Alone	46	2.6 (0.8–8.0)

Drugs listed were those prescribed at discharge from hospital.

the presence or risk of IHD should not influence the choice of conventional diabetes treatment regimen in general or of sulfonylurea drug in particular.

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