Long-Term Survival After Acute Myocardial Infarction and Relation to Type 2 Diabetes and Other Risk Factors

Address for correspondence:
Stephen Fava, MD
Diabetes and Endocrine Centre
Mater Dei Hospital
Msida, Malta
stephen.fava@um.edu.mt

Mark Gruppetta MD, MRCP(UK); Neville Calleja MD, MSc; Stephen Fava MD, FACP, FEFIM, FRCP, PhD
Diabetes and Endocrine Centre, (Gruppetta, Fava), Mater Dei Hospital, Msida, Malta; University of Malta, Department of Medicine, University of Malta (Fava) Department of Public Health, University of Malta (Calleja, Fava), Msida, Malta

ABSTRACT

Background: Diabetes mellitus (DM) is well established as a short-term prognostic indicator after myocardial infarction (MI), but little long-term data are available.

Hypothesis: The objective of the study was to assess the impact of DM and other patient characteristics at baseline on long-term mortality after acute MI.

Methods: Patients who were hospitalized with MI from December 1990 to November 1992 were recruited. Baseline data were recorded and patients were followed up through January 31, 2008, to assess their survival rates. Survival curves were generated by the Kaplan-Meier method. The main outcome measure was long-term survival (median 16.6 y).

Results: The study followed 337 patients (mean age 66.4 y, 61.1% men) for a median of 16.6 years. Using Cox regression analysis, survival was associated with history of MI (hazard ratio [HR]: 1.47, $P = 0.016$), DM at baseline (HR: 1.31, $P = 0.038$), and age (HR: 1.061 for each additional year, $P < 0.001$). By multivariable regression, cardiovascular mortality was also associated with previous MI (HR: 1.58, $P = 0.017$), DM at baseline (HR: 1.69, $P = 0.001$), and age (HR: 1.075 for each additional year, $P < 0.001$). There was no statistically significant difference between the HRs for history of MI and history of DM.

Conclusions: Diabetic patients with MI have a higher long-term all-cause and cardiovascular mortality. Our data also show that in patients with MI, DM confers the same level of risk as a previous MI. This extends to patients with documented MI, our concept of diabetes being a coronary heart disease equivalent. Based on this and on data from the literature, we propose that it would be more accurate to consider DM as an MI equivalent rather than a coronary heart disease equivalent.

Introduction

Diabetes mellitus (DM) is a major risk factor for coronary heart disease (CHD) mortality.[1] Several studies have also shown that DM is associated with decreased survival after acute myocardial infarction (MI).[2–4] The large thrombolysis trials have demonstrated that although this therapy is effective in patients with DM, mortality remains higher.[5–8]

However, these studies usually limit themselves to short follow-up, ranging from 28 days to 1 year in most instances. Few data exist with respect to long-term follow-up. In a nationwide study of patients experiencing a first MI in Holland, Koek et al reported higher 5-year mortality in diabetic subjects.[9] The study with longest follow-up period is the Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT), which found DM to be an independent predictor of 10-year mortality after MI.[10]

The aim of this study was to assess the impact of DM and other prognostic indicators on all-cause and cardiovascular mortality during long-term follow-up (median 16.6 y; range, 15.3–17.2 y) of a cohort of patients who had had an MI.

Methods

In total, 361 patients who had had an MI, with or without ST-segment elevation, were recruited in the study between December 1990 and November 1992. All of these patients were admitted in a general acute medical hospital (Saint Luke's Hospital, Pietà, Malta). The study protocol was as previously described.[4] Briefly, data were collected at baseline with regard to age, gender, medical history, smoking history, and treatment in the index admission, including thrombolysis. Plasma glucose, glycated hemoglobin A_{1c} (HbA_{1c}), serial creatine kinase (CK), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides were also measured. The diagnosis of DM was based on a previous history of DM or baseline laboratory examinations. The presence or absence of left ventricular failure (LVF; Killip classes II–IV) was assessed by a single observer. Informed consent was obtained from all patients.

Patients were followed up until January 31, 2008. Complete data were available on 337 patients (94% of the

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Clin. Cardiol. 33, 7, 424–429 (2010)
Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20776

Received: January 24, 2010
Accepted with revision: March 11, 2010

original cohort); data were incomplete or missing in 24 patients, who were excluded from the analysis. Survival data were collected for each patient from the national mortality register; this was used to assess their survival rates, all-cause mortality, and mortality from cardiovascular-related causes.

Statistical Analysis

Survival curves were generated by the Kaplan-Meier method. To test significance between 2 groups, log-rank tests were used for categorical variables and Cox regression analysis was used for continuous variables.

The primary endpoint of the study was all-cause mortality. Associations between variables and mortality were assessed using stepwise multivariate Cox regression. The proportional hazard for mortality with time was assessed with Cox regression. Subject age was entered as a continuous variable. Multivariate Cox regression (SPSS software, version 15; SPSS Inc., Chicago, IL) was used to determine a hazard ratio (HR) that was corrected for possible confounding variables. The regression model was built by initially including factors with significant or near-significant ($P < 0.10$) univariate associations and also factors potentially confounding the associations. Final modeling used a backward stepwise approach. HRs and 95% confidence intervals (CIs) are presented; a P value ≤ 0.05 was considered to be statistically significant. The effect of DM on survival time was also examined by linear multivariate regression.

Results

Baseline Patient Characteristics

The mean patient age at baseline was 66.4 years, and 61.1% were men. DM was present in 47.5% (all type 2), 39% had a history of CHD, 18.3% had had a previous MI, and 44.2% were nonsmokers. Twenty-four percent had LVF during the index admission. Baseline characteristics are summarized in Table 1. Of the patients with DM, 55 (34.4%) were on insulin.

Table 1. Characteristics of Patients With and Without History of DM at Baseline

	With History of DM at Baseline	Without History of DM at Baseline	Statistical Significance
n	160	177	
Baseline characteristics			
Gender (M%)	60.0	62.1	$P = 0.686$
Mean age (y)	66.1	66.6	$P = 0.630$
Smokers (%)	20.5	37.0	$\chi^2 = 11.5$, $P = 0.003$
Ex-smokers (%)	26.9	23.4	
Nonsmokers (%)	52.6	39.6	
History of HT	37.0	33.2	$P = 0.496$
Type of MI			
Q-wave MI (%)	71.9	73.4	$P = 0.747$
Non–Q-wave MI (%)	28.1	26.6	
Onset of LVF during index admission (%)	29.0	18.6	$P = 0.029$

Abbreviations: DM, diabetes mellitus (type 2); HT, hypertension; LVF, left ventricular failure; MI, myocardial infarction; n, number of patients.

Long-Term Mortality Outcomes

During a median follow-up of 16.6 years (range, 15.3–17.2 y), 244 (72.4%) of the 337 patients died and the overall mean survival of the entire cohort was 9.6 years (95% CI: 8.91–10.27 y). Unadjusted Kaplan-Meier survival was worse for LVF during the index admission ($P = 0.008$), but there were no statistically significant differences for previous CHD ($P = 0.104$) or previous MI ($P = 0.07$). There were also no significant or near-significant associations with baseline total cholesterol, HDL-C, triglycerides, smoking status at baseline, or peak CK during the index admission. DM was an independent predictor of median survival time, when adjusted for age, gender, and previous MI ($P = 0.049$) on linear multivariate regression. Table 2 compares the effect of DM and prior MI at baseline on survival.

Using Cox regression analysis, mortality was associated with the following covariates (Table 3): prior MI (HR: 1.47, 95% CI: 1.07–2.04, $P = 0.016$), history of DM (HR: 1.31, 95% CI: 1.02–1.69, $P = 0.038$), and age (HR: 1.061, 95% CI: 1.04–1.08 for each additional year; $P < 0.001$). There were no statistically significant differences between the hazard ratios of either all-cause or cardiovascular mortality for prior MI and that for DM at baseline (Table 2). The covariates of gender, LVF during the index admission, LDL-C, CK peak levels, and use of thrombolytic therapy did not meet criteria for retention in the model and did not significantly affect the results after adjustment for the retained covariates. Cardiovascular mortality was also associated with a previous MI (HR: 1.58, $P = 0.017$), DM at baseline (HR: 1.69, $P = 0.001$), and age (HR: 1.075 for each additional year, $P < 0.001$).

Table 2. Patient Groups and Unadjusted Survival Rates

	History of DM and MI	History of DM Only	History of MI Only	No History of DM or MI
n	67	91	63	113
Unadjusted mean survival, y (95% CI)	8.24 (6.75–9.73)	9.57 (8.33–10.81)	9.68 (8.05–11.31)	10.3 (9.11–11.46)
Unadjusted median survival, y (95% CI)	6.58 (3.03–10.12)	9.04 (7.07–11.02)	10.28 (6.86–13.70)	10.83 (7.99–13.66)
5-y survival (%)	61.2	70.3	69.8	73.5
10-y survival (%)	38.9	44.0	52.4	54.0
15-y survival (%)	25.4	33.0	31.7	38.1

Abbreviations: CI, confidence interval; DM, diabetes mellitus (type 2); MI, myocardial infarction; n, number of patients.

Table 3. Hazard Ratios and 95% Confidence Intervals for Statistically Significant Variables

		Hazard Ratio	95% CI	*P* Value
All-cause mortality	History of DM at baseline	1.31	1.02–1.69	0.038
	Age (each additional year)	1.06	1.04–1.08	<0.001
	Prior MI	1.47	1.07–2.04	0.016
Cardiovascular-related deaths	History of DM at baseline	1.69	1.25–2.33	0.001
	Age (each additional year)	1.08	1.05–1.20	<0.001
	Prior MI	1.58	1.09–2.27	0.017
All-cause mortality in DM subgroup	Age (each additional year)	1.06	1.03–1.08	<0.001
	Prior MI	1.68	1.05–2.70	0.031

Abbreviations: CI, confidence interval; DM, diabetes mellitus (type 2); MI, myocardial infarction.

Multivariable regression in the prespecified subgroup of DM patients (Table 3) revealed significant associations of age (HR: 1.056, 95% CI: 1.03–1.08 for each additional year, $P < 0.001$) and prior MI (HR: 1.675, 95% CI: 1.05–2.70, $P = 0.031$) with survival. The HR in patients with both DM and prior MI was 2.19 ($P = 0.015$) compared with patients who had neither. Plasma glucose and HbA_{1c} on admission did not meet the criteria for retention in the model and did not significantly affect the results after adjustment for the retained covariates. Figure 1 shows the Kaplan-Meier curves for all-cause and cardiovascular mortality in the DM subgroup.

Discussion

In our study, we found that DM at baseline is associated with higher long-term (>15 y) all-cause and cardiovascular mortality in patients with MI. To our knowledge, no previous studies have reported such long-term data. Although many authors have demonstrated higher mortality in diabetic patients with MI, few studies have had follow-up periods of more than 2 years. In our study, the median follow-up was 16.5 years. This long follow-up, coupled with the very small number of patients who were lost to follow-up (data reflect 94% of the original cohort) and the high prevalence of DM in Malta, put us in a unique position to study the effect of DM on the long-term outcome after MI. Our results also show that the survival curves of the DM and non-DM subjects separate quite early but remain divergent throughout the follow-up period (Figure 1). This illustrates the need for early, aggressive intervention in diabetic patients with acute MI. Our data further show that, as expected, older age and previous MI are associated with poorer survival in the whole cohort as well as in the DM subgroup.

Although LVF during the index admission was associated with long-term mortality in univariate analysis, this did not persist in multivariate analysis after adjustment for other covariables. This is probably because the effect of other factors such as advancing age, DM, and previous MI is partly mediated through left ventricular dysfunction. It should also be noted that we only assessed LVF on clinical grounds (Killip classification). More sensitive measures of left ventricular dysfunction, such as echocardiography or B-type natriuretic peptide, might have given more positive results. The latter was not available at the time of commencement of the study.

We also found no association of mortality with gender. Although most authors have reported that females have higher early mortality after MI,[11,12] this may largely be attributable to differences in known risk factors[12] and possibly to higher prehospital mortality in males.[13] Since our study was conducted on a small island where travel times

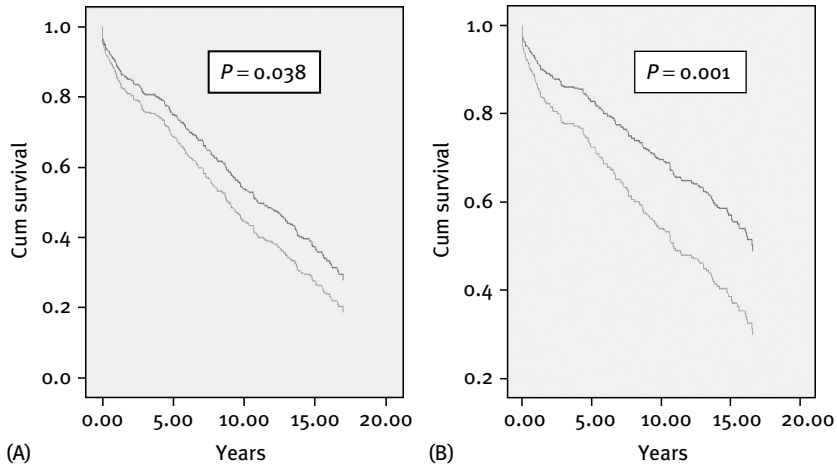

Figure 1. Multivariate Cox regression comparing overall survival (panel A) and survival from cardiovascular deaths (panel B) of patients with diabetes (grey) and those without diabetes (black) at baseline. Abbreviations: CUM, cumulative.

to hospital are shorter, prehospital mortality may be lower than elsewhere. The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO)- 1 trial also did not find any gender difference in mortality at 1 year.[11]

Haffner et al found that the risk of death from CHD for subjects with DM and without prior MI was similar to that of nondiabetic subjects with prior MI after adjustment for age and gender (HR: 1.4, 95% CI: 0.7–2.6).[14] However, there were only 69 nondiabetic subjects in the study who had had a previous MI; therefore, as has been suggested previously,[15] the study may have been underpowered to detect differences between the 2 groups. The same authors have recently confirmed their findings in an 18-year prospective follow-up study.[16] The Renfrew and Paisley Survey has also reported similar results after 25 years of follow-up.[17] However, the authors largely based the diagnosis of DM on a self-reporting questionnaire, with the limitations associated with this approach. The Nurses' Health Study has likewise found that DM carries a risk of CHD mortality similar to previous MI.[15] The strength of the latter study is the large number of subjects studied. However, the diagnoses of both DM and MI were also based on self-completed questionnaires.

In contrast, the diagnosis of DM in our study was based on a previous history of DM and baseline laboratory examinations. Furthermore, we studied a different cohort of patients, namely those with an acute MI. Our data show that in such subjects, DM confers the same risk of all-cause and cardiovascular mortality as a prior MI (Table 2). To our knowledge, this has not been previously reported; other authors have studied the general diabetic population. Our results therefore extend the concept of DM being a CHD equivalent. Based on our data taken in context of previous studies, it may be more accurate to refer to DM as an MI equivalent, because it confers the same risk as a previous MI both in patients with and without known coronary artery disease. However, this concept of CHD or MI equivalence should not detract from the fact that subjects with both CHD and DM are at an especially high risk. In our study, diabetic subjects with an acute MI had a mortality of 35% at 5 years, 57% at 10 years, and 70% at 15 years (Figure 1). The HR in subjects with both DM and prior MI was 2.19. Furthermore, in the DM subgroup with an acute MI, previous MI was significantly associated with increased all-cause and cardiovascular mortality. Therefore, such patients should be targeted for aggressive intervention.

Our primary endpoint was all-cause mortality. This is a hard endpoint which can be accurately ascertained. On the other hand, cardiovascular deaths could only be determined from death-certificate data. This has been reported to have a 65%- positive predictive value for cardiovascular disease when compared with autopsy data.[18] However, our data are internally consistent.

As with other long-term studies, it is difficult to be certain how modern treatment would have influenced results. In particular, primary angioplasty, low-molecular-weight heparin, and newer antiplatelet and antithrombotic agents were not available at the time of commencement of the study. Short-term studies indicate that although primary angioplasty is beneficial in diabetic patients, it is unable to reduce the risk to that of non-diabetic subjects.[19,20] Indeed, there is evidence that its beneficial effect might disappear by 3 years in subjects with DM.[21] Furthermore, thrombolytic therapy remains a viable alternative to angioplasty where the latter cannot be performed expeditiously. Even in many trials, more patients with MI receive thrombolytic therapy than undergo angioplasty.[22,23] This figure is likely to be higher in the real world. There is also no

convincing evidence that antiplatelet glycoprotein IIb/IIIa agents reduce survival in diabetic patients with MI.[24,25] Although Théroux et al reported a beneficial effect of these agents, they studied a mixed population that included both patients with MI and unstable angina.[26] Low-molecular-weight heparin may improve short-term[27] but not long-term[28] survival. Data on clopidogrel use in diabetic patients after MI is restricted to short-term registry data[29] with no clinical-trial data being available at present. Wiviott et al recently reported that prasugrel may be superior to clopidogrel in diabetic patients.[30] Fondaparinux (a direct factor Xa inhibitor) may reduce short-term mortality,[31] but there are no data on with respect to DM or long-term follow-up.

Conclusion

Our data show that DM, previous MI, and age are independent predictors of long-term (>15 y) all-cause and cardiovascular mortality after acute MI. DM was associated with the same level of risk as a previous MI. Based on this and on other data from the literature, we propose that it would be more accurate to consider diabetes as an MI equivalent rather than a CHD equivalent. In the DM subgroup, age and previous MI were also independent predictors of long-term (>15 y) mortality.

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Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20776

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Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20776