The Impact of Diabetes on Survival Among Patients With First Myocardial Infarction

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OBJECTIVE — The purpose of this paper is to estimate the impact of diabetes on survival among patients with first acute myocardial infarction, using data from the World Health Organization (WHO) Monitoring Trends and Determinants of Cardiovascular Disease (MONICA) Project in Newcastle, New South Wales, Australia.

RESEARCH DESIGN AND METHODS — The WHO MONICA Project is a community-based surveillance system that monitors coronary heart disease morbidity and mortality. All patients with suspected coronary events were observed for 28 days after the onset of symptoms.

RESULTS — Of 5,322 patients with acute myocardial infarction and no previous history of ischemic heart disease (3,643 men and 1,679 women), 333 men (9%) and 224 women (13%) had a history of diabetes. The age-adjusted 28-day case fatality for women with diabetes (25%) was significantly higher than for women without diabetes (16%); relative risk 1.56 (95% CI: 1.19–2.04). The difference for men was also significant (25% with diabetes and 20% without diabetes); relative risk 1.25 (95% CI: 1.02–1.53). Age-specific case fatality increased significantly with age in both men and women without diabetes, but systematic age effects were not so apparent in patients with diabetes. Case fatality significantly decreased over the study period in patients without diabetes, but not among the diabetic patients.

CONCLUSIONS — The increased risk of death in the diabetic patients remained after accounting for their poorer risk factor profiles; even if they reached the hospital alive, diabetic patients were also less likely to survive than nondiabetic patients. The relative impact of diabetes on survival is greater in women than in men.

It is well established that diabetes is associated with increased risk of coronary heart disease morbidity and mortality (1–4). In addition, there is evidence that patients with diabetes have a poorer prognosis than patients without diabetes after a myocardial infarction (MI) (5–14). Because many studies suggest that diabetic patients are more likely to have increased levels of risk factors for coronary heart disease than nondiabetic patients (15,16), it is not clear whether poorer survival among diabetic patients after MI is attributable to diabetes per se or unfavorable risk factor profiles.

In hospital-based studies there is always a possibility that different patterns of hospitalization for suspected MI among patients with or without diabetes may influence survival. Also for coronary disease, many deaths occur before the patient can reach the hospital (17). There are few population-based studies that investigate the effects of diabetes on survival of MI patients. The World Health Organization (WHO) Monitoring Trends and Determinants of Cardiovascular Disease (MONICA) Project is a population-based monitoring system measuring trends in coronary heart disease morbidity, mortality, and risk factors (18). This provides an opportunity to compare case fatality from MI among patients with and without diabetes from a community perspective.

RESEARCH DESIGN AND METHODS

— Residents aged 30–69 years of the lower Hunter Region of New South Wales, Australia, made up the study population. All cases of suspected heart attack or coronary death in this population were registered. Diagnostic information, medical history, and risk factor status were obtained from patients interviewed while still in the hospital, from hospital records, and from the certifying doctor, autopsy reports, relatives, and other informants for deceased patients. Patients with no previous history of MI or other manifestations of ischemic heart disease (e.g., angina) and who met the criteria of the WHO MONICA Project for definite or possible (nonfatal or fatal) MI or coronary death with insufficient information for further classification were included in the study (19). Over the study period from 1 January 1985 to 31 March 1994, there were 5,322 patients who met these inclusion criteria.

The data collected included age, sex, medical history, smoking status, and survival status at 28 days from onset of symptoms. Patients were considered diabetic if they had a history of the disease (self-reported or stated in medical records) or were taking insulin and/or oral hypoglycemic agents before the acute event. There were 26 patients not previously known to be diabetic who were diagnosed during their hospital admission and were discharged from the hospital with persisting diabetes; they were classified as diabetic for this study. The MONICA data did not include information about the type of diabetes. Patients told by a doctor or another medical professional that they had high blood pressure were classified as having a history of hypertension. Similarly, patients who were told they had high cholesterol were classified as having a history of hyper-

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MI, myocardial infarction; MONICA, Monitoring Trends and Determinants of Cardiovascular Disease; WHO, World Health Organization.

Table 1—*Prevalence (per 100) of diabetes among 5,322 patients with first acute MI or coronary death by sex and age*

Age (years)	Men	Percentage	Women	Percentage
30–39	6/214	2.8	3/44	6.8
40–49	40/724	5.5	14/207	6.8
50–59	107/1,145	9.3	60/469	12.8
60–69	180/1,560	11.5	147/959	15.3
Total	333/3,643	9.1	224/1,679	13.3
Age-adjusted		9.4		12.6

Age-adjusted to the total population of cases of first MI or coronary death without a history of previous MI. The χ^2 test for linear trend was $P < 0.001$.

cholesterolemia. Actual measurements of blood pressure or cholesterol were not made for the study. When the patient died out of the hospital or within the first 24 h after hospitalization, data on risk factors and medical history were sought from medical records or other sources but were sometimes unobtainable. Overall, information was obtained from patients in 70% of the cases, from other sources in 23%, and was missing in 7% of cases.

The outcome was survival at 28 days after onset of the acute coronary event, assessed by review of hospital records and surveillance of death certificates. Age-adjusted case fatality, prevalence of diabetes, and other risk factors were calculated by direct method using the age distribution of all study patients as the standard population. Univariate comparisons between patients with and without diabetes were assessed using the χ^2 test for categorical variables. Because the distribution of patient ages was very skewed, Wilcoxon's test to compare medians was used. Multiple logistic regression was used to assess the combined effects of diabetes and other risk factors on case fatality.

RESULTS — The age-adjusted prevalence of diabetes in patients with first MI or coronary death was 9.4 per 100 in men and 12.6 per 100 in women. The prevalence of diabetes increased significantly with age in both sexes ($P < 0.001$ for linear trend) (Table 1).

In both sexes, diabetic patients had significantly different risk factor patterns compared with nondiabetic patients. Diabetic patients were older and had a higher prevalence of hypertension history and lower prevalence of current smoking, although the difference in smoking prevalence was not statistically significant (Table 2).

In both sexes, 28-day case fatality decreased significantly with the year of onset of coronary event symptoms in nondiabetic patients, whereas there were no apparent trends in case fatality in diabetic patients (Table 3).

Age-adjusted case fatality in diabetic patients was significantly higher than in nondiabetic patients in both sexes. The relative risk for men was 1.25 (95% CI: 1.02–1.53) and for women was 1.56 (95% CI: 1.19–2.04). Among nondiabetic patients, case fatality increased significantly with age for both sexes. Among diabetic patients, trends of case fatality with age were less apparent in part because of the small numbers of death in some age-groups. Age-specific case fatality in men with diabetes was higher than in men without diabetes, but the differences decreased with age. In women, differences in age-specific case fatality did not show consistent patterns (Table 4).

Logistic regression analysis showed that for men, case fatality increased significantly with age, decreased with calendar year of onset, and was lower in men with a history of hypercholesterolemia. Once these factors were taken into account, the increased risk associated with diabetes did not change much, but was no longer statistically significant (R^2 = 1.22, 95% CI: 0.91–1.62). For women, case fatality increased significantly with age and was higher in current smokers and lower in women with a history of hypercholesterolemia. Even with adjustment for these factors, the increased risk associated with diabetes was still statistically significant (R^2 = 1.89, 95% CI: 1.31–2.72) (Table 5).

CONCLUSIONS — The findings of this study are that diabetes is associated with lower probability of 28-day survival among patients with first MI or coronary death; the association was statistically significant for women but not for men. Because all patients, including those who died out of the hospital, were registered from the whole community, selection bias is unlikely to have occurred (20). Inclusion only of patients without a history of MI or other manifestations of ischemic heart disease (e.g., angina) should have reduced confounding by differences in medical care. However, some misclassification bias is possible for patients who died, because diabetes is believed to be underreported on doctors' death certificates (21). This bias would lead to underestimation of the impact of diabetes on case fatality. Patients with unrecognized diabetes, who do not die, could also distort the study results. In fact, 26 hyperglycemic patients were diagnosed for the first time during hospitalization for MI. One previous study reported that hyperglycemia during hospitalization is a temporary phenomenon induced by stress (22), while other studies suggested that previously undiagnosed diabetes is a more likely explanation than stress-induced hyperglycemia (23,24). Nevertheless, the prevalence of undiagnosed diabetes in MI patients (0.5%) in this study was much lower than reported in other

Table 2—*Characteristics of patients with and without diabetes: median age and age-adjusted percentages for men and women*

	Men			Women		
	With diabetes	Without diabetes	Difference (95% CI)	With diabetes	Without diabetes	Difference (95% CI)
n	333	3,310		224	1,455	
Age	61 (54, 66)	57 (49, 63)*		63 (57, 67)	61 (54, 65)*	
Smoking	38	44	−6 (−15–3)	26	38	−12 (−25–1)
Hypertension	57	44	12 (5–20)	65	56	9 (1–17)
High cholesterol	30	30	0 (−10–10)	38	32	6 (−6–19)

Data for age are median (first quartile, third quartile). Data for smoking, hypertension, and high cholesterol are age-adjusted percentages. Data were missing for up to 4% of cases for smoking, 3% for hypertension, and 12% for hypercholesterolemia. *$P < 0.001$ by Wilcoxon's test.

Table 3—*Case fatality by year of onset of coronary event symptoms and diabetes status*

Year of symptom onset	Men		Women	
	With diabetes	Without diabetes	With diabetes	Without diabetes
1985	25.0	26.0	13.3	25.5
1986	25.0	22.8	37.5	22.4
1987	17.2	22.9	22.2	12.5
1988	36.1	20.0	50.0	16.8
1989	26.7	18.1	37.0	18.7
1990	34.9	17.3	22.2	17.3
1991	33.3	17.1	34.6	12.3
1992	20.0	17.8	24.0	16.1
1993	10.8	11.5	13.8	14.3
1994*	16.7	13.1	0.0	6.9
Trends†	$P = 0.42$	$P < 0.001$	$P = 0.42$	$P < 0.001$

Data are %; *excluded from test for trend because cases were not registered for the full calendar year; †χ^2 test for linear trend.

studies (4.5–5.3%), possibly because the diagnosis of diabetes in previous studies was made by an oral glucose tolerance test (23,25), whereas this study relied on case findings in the hospital. Thus, the true prevalence of diabetes at the time of MI or coronary death in this study may be underestimated. It therefore seems possible that the impact of diabetes on survival among MI patients is underestimated in both sexes (5, 25).

To examine whether diabetes had an independent influence on survival after MI, adjustment had to be made for possible confounders. After multivariate analysis to adjust for other factors, diabetes was statistically significantly associated with increased risk of death in women, and the effect was also apparent (but was not statistically significant) in men. These findings are consistent with the results of many other studies in women (5,6,8,10–14) and also consistent for men if the magnitude of relative risk or odds ratios is considered rather than just the statistical significance (6,8,10,12–14,26).

Among patients without diabetes, there was a marked decrease in case fatality in both sexes over the study period; however, no such trends were apparent in those with diabetes. The change in case fatality is likely to be related to improved treatment; especially, thrombolysis and use of beta blockers and aspirin. In this study, younger patients <50 years old with diabetes were more likely to die than younger patients without diabetes. The difference was less pronounced with increasing age. Previous studies have reported a similar result, with the risk ratio associated with diabetes declining with increasing age (9,13,27). Thus, it appears that diabetes modifies the effect of age on survival among MI patients in both sexes.

Current smoking was associated with higher case fatality in men and women (with the effect being statistically significant in women) (12,28,29). There is an apparent decreased risk of dying in patients with a known history of raised cholesterol, compared with the group without such an established history in this study. This is potentially due to strong associations with the other risk factors considered. Patients with hypercholesterolemia were more likely to have hypertension and less likely to be current smokers than those who did not report they had ever been told they had high cholesterol. Prevalence of hypercholesterolemia also increased with calendar year of the study as testing became more widespread in the community. Therefore, confounding with other explanatory variables may be the reason for the effect of raised cholesterol estimated in this study. Other possible explanations include misclassification (patients in good health may not have known they had high cholesterol), differential availability of data on hypercholesterolemia for patients who died, compared with those who survived, or quick and more intensive treatment of patients with a known history of high cholesterol.

It was also evident that the prevalence of other risk factors was higher among diabetic patients than among nondiabetic patients, especially for women. This concurs with the findings of Phillips et al. (30). This is because the risk factors for diabetes are also risk factors for coronary heart disease. There is conclusive evidence that atherosclerosis and diabetes develop coincidentally, in parallel or even in reversed sequence (31,32). Thus, the excess risk of death in patients with diabetes is likely to be due to more advanced disease, less readily prevented by risk factor modification. In light of the findings reported here, it is suggested that evaluation of the benefits of intensive risk factor reduc-

Table 4—*Case fatality for patients with and without diabetes by age and sex*

Age (years)	Men			Women		
	With diabetes	Without diabetes	Relative risk (95% CI)	With diabetes	Without diabetes	Relative risk (95% CI)
n	333	3,310		224	1,455	
30–39	16.7	9.1	1.82 (0.29–11.49)	0.0	17.1	0
40–49	22.5	10.2	2.20 (1.19–4.07)	35.7	8.8	4.05 (1.76–9.36)
50–59	24.3	17.2	1.41 (0.98–2.02)	6.7	10.5	0.63 (0.24–1.70)
60–69	27.2	26.6	1.02 (0.79–1.32)	35.4	22.2	1.60 (1.24–2.06)
Crude	25.5	19.1	1.33 (1.09–1.62)	27.2	17.0	1.60 (1.26–2.04)
Age-adjusted	25.0	20.0	1.25 (1.02–1.53)	25.0	16.0	1.56 (1.19–2.04)
Age trend	$P = 0.38$	$P < 0.001$	—		$P < 0.001$	

Data are % or 95% CI (range). Test for age trend of women with diabetes was not performed because of small numbers of deaths in some age-groups.

Table 5—*Multiple logistic regression modeling of the effect of diabetes on case fatality of patients, adjusted for other factors*

	Men		Women	
Explanatory variables	Relative risk	95% CI	Relative risk	95% CI
Diabetes	1.22	(0.91–1.62)	1.89	(1.31–2.72)
Age*	1.63	(1.46–1.82)	1.75	(1.43–2.14)
Year of symptom onset*	0.94	(0.91–0.97)	0.97	(0.92–1.02)
Smoking	1.17	(0.98–1.40)	1.50	(1.12–2.00)
Hypertension	1.12	(0.94–1.33)	0.91	(0.69–1.21)
Hypercholesterolemia	0.71	(0.58–0.87)	0.47	(0.34–0.66)

Data are % or 95% CI (range). *Age (in 10-year groups) and calendar year of onset of symptoms were treated as continuous variables.

tion and of aggressive treatment of diabetic patients is warranted to reduce case fatality from MI, in line with reductions recently attained for nondiabetic patients.

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