Sex Differences in the Prognostic Importance of Diabetes in Patients With Ischemic Heart Disease Undergoing Coronary Angiography

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OBJECTIVE — Women with ischemic heart disease have poorer outcomes than men and are suggested to have greater risk associated with diabetes. We evaluated the prognosis associated with diabetes, in analyses stratified by sex, to determine whether similar differences are seen in a large unselected cohort of patients.

RESEARCH DESIGN AND METHODS — Using the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH), a clinical data collection and follow-up initiative capturing all patients undergoing cardiac catheterization in Alberta, Canada, the relative significance of diabetes on long-term survival in 13,152 men and 4,249 women was evaluated in patients presenting with or without myocardial infarction and according to first treatment received.

RESULTS — The 1-year mortality rates were 4.7% and 6.8% in men and women ($P < 0.001$), 4.1% and 7.4% in nondiabetic and diabetic men ($P < 0.001$), and 5.8% and 9.6% in nondiabetic and diabetic women, respectively ($P < 0.001$). The risk-adjusted Cox proportional hazard ratios associated with diabetes in myocardial infarction were 1.03 in men and 1.20 in women. The diabetes hazard ratios for percutaneous coronary intervention were 1.28 in men and 1.40 in women, 1.23 in men and 1.32 in women for bypass surgery, and 1.26 in men and 1.31 in women for medical therapy (P = NS for all diabetes hazard ratio comparisons between men and women).

CONCLUSIONS — Hazard ratios quantifying the adverse prognosis associated with diabetes in patients undergoing angiography are consistently higher among women than men, but the differences across sexes are not statistically significant. These slight sex differences noted in the APPROACH registry are similar to previously reported findings and may be clinically important.

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Abbreviations: APPROACH, Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Ischemic heart disease continues to be the leading cause of morbidity and mortality in North America (1). Women with ischemic heart disease are known to have a poorer prognosis than men with ischemic heart disease. Reasons for poor outcomes include older age, the presence of significant comorbidities, more severe clinical presentations, and higher rates of in-hospital complications (2). Additionally, early registry studies (3–5) have suggested that the presence of diabetes is of greater importance in women, particularly influencing outcome after myocardial infarction. However, many of these studies used selected patient populations or sparsely detailed administrative databases.

We have developed a large, population-based, clinical registry that captures detailed clinical information for all patients undergoing cardiac catheterization in the Canadian province of Alberta (6). This database provides a unique opportunity to evaluate outcomes in a large cohort of patients with ischemic heart disease. The goal of the present analysis was to evaluate the prognosis associated with diabetes, in analyses stratified by sex, in a general cohort of patients undergoing coronary angiography. Sex differences in the influence of diabetes on outcome were also assessed in subgroups, first according to clinical presentation (with or without myocardial infarction) and next according to first assigned treatment (medical therapy, percutaneous coronary intervention, or coronary artery bypass graft surgery).

RESEARCH DESIGN AND METHODS

— The Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) is a clinical data collection initiative that captures all patients undergoing cardiac catheterization in the province of Alberta. Cardiac care in Canada is typified by a lower rate of use of coronary angiography and revasculariza-

tion procedures than in the U.S. (7). However, based on a recent examination of cardiac procedure use (8), Alberta has among the highest use of revascularization procedures post myocardial infarction in Canada (36%). Furthermore, in Calgary, one of the two cities with cardiac catheterization facilities in Alberta, 76.3% of patients discharged with a diagnosis of acute myocardial infarction undergo angiography. For the present study, data from patients who underwent cardiac catheterization from 1 January 1995 to 31 December 1998 were used. Patients undergoing cardiac catheterization for investigation of valvular heart disease and those found to have no significant coronary artery disease were excluded from this analysis. The database contains detailed clinical information, including patient's age, sex, ejection fraction, and the presence or absence of previous myocardial infarction, congestive heart failure, cerebrovascular disease, peripheral vascular disease, chronic pulmonary disease, elevated creatinine, renal dialysis, hyperlipidemia, hypertension, liver disease, gastrointestinal disease, or malignancy. Indication for the procedure (for example acute myocardial infarction, acute coronary syndrome, or stable angina) is also recorded. The APPROACH database also tracks therapeutic interventions, such as previous thrombolytic therapy and previous or subsequent revascularization procedures. Extent of coronary artery disease is documented as the number of vessels with stenoses >50%, with lesions in the proximal left anterior descending artery considered separately. Follow-up mortality is ascertained through semiannual linkage to data from the Alberta Bureau of Vital Statistics.

Diabetes is considered present if mentioned in a patient's hospital chart or if reported by the patient at the time of catheterization. At the time of data analysis, an additional "data enhancement" procedure occurs to improve the validity of APPROACH data used in study analyses such as those presented here. The data enhancement process involves linkage of APPROACH clinical data to administrative hospital discharge data to verify the validity of information recorded in APPROACH and to fill in any missing data elements in the clinical database. This validated methodology has been previously described (9).

Statistical analysis

ANOVA was used to test for baseline differences in age among the groups, and χ^2 tests of independence were used to test for baseline differences among groups for all other variables. Unadjusted and adjusted hazard ratios for diabetes were calculated using Cox proportional hazards models. The variables listed in Table 1 were used in the adjusted models. To obtain hazard ratios for diabetes within clinical and treatment subgroups, a number of interaction terms were assessed in the Cox models. We calculated hazard ratios for diabetes by sex within treatment groups (interaction terms in model: sex by diabetes, sex by treatment, and sex by diabetes by treatment). We also calculated hazard ratios for diabetes by sex within subgroups of patients with versus without myocardial infarction as the indication for catheterization (interaction terms in model: sex by diabetes, sex by myocardial infarction, and sex by diabetes by myocardial infarction). The variances of the log of the hazard ratios were used for constructing 95% CIs around the hazard ratios. These variances were calculated by applying the contrast terms associated with the hazard ratios to the variance-covariance matrix of the regression coefficients from the Cox models (10,11). All analyses were done using SPlus 5 for Linux, version 5.1 (Insightful, Seattle, WA).

RESULTS — After exclusion of patients with valvular heart disease and those without significant coronary artery disease, a total of 17,401 patients with ischemic heart disease underwent cardiac catheterization from 1 January 1995 to 31 December 1998. Table 1 shows the baseline characteristics of the men and women in the entire cohort according to presence or absence of diabetes. Diabetic patients of both sexes were more likely to have low ejection fractions and were more likely to have hypertension, renal insufficiency, peripheral vascular disease, cerebrovascular disease, and chronic obstructive pulmonary disease. Women with diabetes were more likely to report a history of congestive heart failure, previous myocardial infarction, or revascularization procedure than women without diabetes. This was not seen in men. Both groups of diabetic patients were found to have more three-vessel disease on angiography.

Mortality rates at 1 year were 4.7% in men and 6.8% in women ($P < 0.001$). Mortality rates were 4.1% and 7.4% in nondiabetic and diabetic men ($P < 0.001$) and 5.8% and 9.6% in nondiabetic and diabetic women, respectively ($P < 0.001$). Figure 1 shows risk-adjusted survival curves extending to 4 years of follow-up. Women have lower survival over time compared with men, particularly the subgroup of patients with diabetes.

Table 2 shows the hazard ratios and 95% CIs for total mortality associated with diabetes for up to 4 years of follow-up. In the general cohort of patients, hazard ratios were 1.92 for men and 1.89 for women. After adjusting for baseline risk factor differences, the hazard ratios were 1.25 in men and 1.34 in women. Table 3 shows hazard ratios associated with diabetes for various patient subgroups. While the hazard ratio comparisons between sexes were not statistically significant, interesting differences between sexes were noted, with women consistently having slightly higher adjusted hazard ratios for diabetes than men. The sex differences in the hazard ratios associated with diabetes were somewhat greater in patients presenting with acute myocardial infarction as the indication for cardiac catheterization (adjusted hazard ratio of 1.03 in men and 1.20 in women). The subgroup analysis by treatment category is also shown. The most striking difference was noted in patients treated with percutaneous coronary intervention, where diabetes was associated with an adjusted hazard ratio of 1.28 in men and 1.40 in women.

CONCLUSIONS — In the present study, we have found a slight sex difference in the hazard ratios associated with diabetes in patients with ischemic heart disease undergoing coronary angiography. Although the hazard ratio differences between sexes are not statistically significant, there is a consistency of difference across subgroups that may be clinically important, particularly in patients presenting with acute myocardial infarction and in those treated with percutaneous coronary intervention. Furthermore, this finding of sex differences in the prognostic importance of diabetes has, to varying degrees, been previously reported.

Coronary artery disease is the leading cause of morbidity and mortality associated with diabetes (3,12). There are a variety of reasons for this, including dyslipidemia, insulin resistance, and hyper-

Table 1—*Baseline characteristics*

	Women			Men		
	No diabetes	Diabetes	*P*	No diabetes	Diabetes	*P*
n	3,175	1,074		10,741	2,411	
Age (years)	66.76	65.68	0.005	62.07	63.58	<0.001
Ejection fraction			<0.001			<0.001
<30	3.9	6.2	—	5.1	8.7	—
30–50	18.0	26.4	—	24.3	29.5	—
>50	59.1	48.9	—	51.9	43.2	—
LV not done	4.5	5.8	—	4.2	5.0	—
Missing	14.5	12.8	—	14.5	13.6	—
CHF	16.2	27.6	<0.001	10.9	22.9	<0.001
Peripheral vascular disease	6.6	11.9	<0.001	6.2	12.2	<0.001
Chronic pulmonary disease	9.7	13.9	<0.001	7.4	9.8	<0.001
Cerebrovascular disease	6.5	11.2	<0.001	5.0	7.8	<0.001
Creatinine >200 mm/l	1.7	5.5	<0.001	1.8	5.6	<0.001
Dialysis	0.7	3.5	<0.001	0.9	3.1	<0.001
Hypertension	58.2	73.6	<0.001	46.2	61.8	<0.001
Hyperlipidemia	43.1	44.5	0.427	44.0	46.8	0.012
Liver/GI	3.3	3.5	0.752	3.0	3.2	0.518
Malignancy	4.0	3.4	0.364	2.9	3.2	0.470
Prior MI	52.1	58.5	<0.001	58.9	60.0	0.350
Prior CABG	5.1	7.0	0.025	9.7	10.5	0.234
Prior PCI	9.9	12.1	0.046	13.3	12.6	0.360
Prior thrombolysis	13.2	10.7	0.038	13.8	10.8	<0.001
Clinical indication			0.385			<0.001
Myocardial infarction	30.2	31.3	—	31.7	30.4	—
Stable angina	26.5	25.4	—	31.3	28.4	—
Unstable angina	34.6	33.1	—	28.8	30.3	—
Other	8.7	10.1	—	8.2	10.9	—
Coronary anatomy			<0.001			<0.001
One-two vessel disease	39.2	26.4	—	29.0	20.3	—
Two vessel + proximal LAD	20.8	17.7	—	20.1	14.7	—
Three vessel disease	19.0	27.2	—	24.0	31.0	—
Three vessel + proximal LAD	12.5	20.5	—	17.1	22.1	—
Left main	8.5	8.2	—	9.8	11.8	—
Death at 1 year	5.8	9.6	<0.001	4.1	7.4	<0.001

Data are percent unless otherwise indicated. CABG, coronary artery bypass graft; CHF, congestive heart failure; GI, gastrointestinal; LAD, left anterior descending; LV, left ventricle; MI, myocardial infarction; PCI, percutaneous coronary intervention.

viscosity. There are also a number of hematologic abnormalities that predispose to thrombosis (13). It is unclear whether these factors act differentially in women versus men, but our findings and those of others suggest that there may be some pathophysiological differences between sexes. Indeed, Haffner et al. (14) have shown that diabetic women tend to be older and tend to have a higher likelihood of associated hypertension than do their male counterparts. Also, the relationship between diabetes and endothelial function may interestingly vary between sexes, as revealed in an elegant study by Steinberg et al. (15) showing that diabetes is an important predictor of endothelial dysfunction in women, while obesity is a more important contributor to endothelial dysfunction in men.

A number of epidemiological studies (2–5) using administrative or small clinical databases confirm the poor outcomes in women with diabetes, particularly following acute myocardial infarction. Others show either no effect of sex (16) or an even greater impact in men with diabetes (17). In a meta-analysis of all eligible prospective cohort studies using the "best data" approach, Lee et al. (18) found a significantly greater relative risk of death related to ischemic heart disease in diabetic women.

Using data from the APPROACH registry, we find slight sex differences in the prognosis of diabetes in patients undergoing cardiac catheterization following myocardial infarction. However, in the present study these differences are of a much smaller magnitude than previously reported. Many of the previous studies used administrative databases with sparse clinical detail or selected patient groups that are not representative at the population level. The major explanation for the attenuated hazard ratios in women with diabetes, however, is likely our large, clinically rich database. APPROACH is unique in that it evaluates an entire collection of patients undergoing cardiac catheterization (i.e., not a sample) and

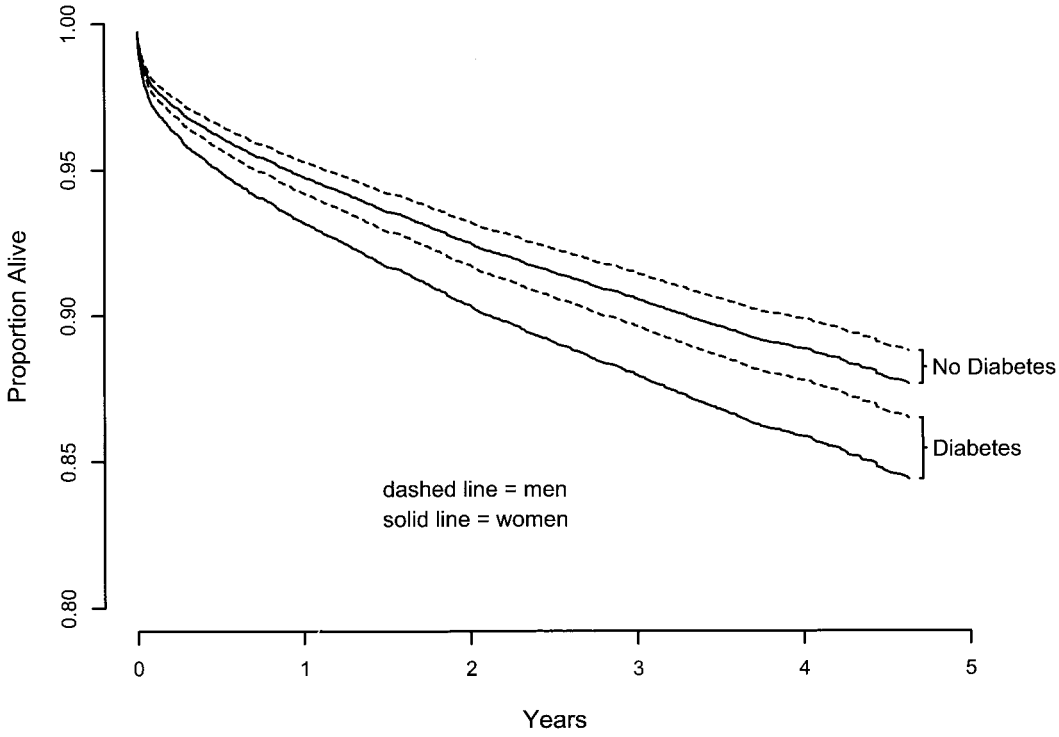

Figure 1—*Adjusted survival curves for mortality up to 4 years.*

contains a wealth of clinical characteristics, including documentation of coronary anatomy. Ghali et al. (19), using the APPROACH database, have previously shown that there was little or no independent association of diabetes with survival after adjustment for adverse clinical risk factors, some of which arise as a result of diabetes. The hazard ratios noted in our study are higher than those found by Ghali et al. (19), primarily because we focused only on patients with obstructive coronary disease.

In our study, diabetic women have particularly poor outcomes when treated with percutaneous coronary intervention, with modest increases in the diabetes hazard ratio compared with men. There is a large body of evidence documenting that diabetic patients have worse outcomes when treated with angioplasty (20–25). Diabetes predisposes patients to higher rates of disease progression and increased restenosis (21). In a long-term follow-up of the Bypass Angioplasty Revascularization Investigation trial, Detre et al. (22) reported that diabetic patients were more likely to suffer acute myocardial infarction over time.

Yet another consideration is that of incomplete revascularization, a scenario that is perhaps more likely to arise when revascularization is done percutaneously as opposed to surgically. Diabetic patients tend to have more extensive and diffuse coronary artery disease and, thus, may have many other significant lesions that are not amenable to percutaneous coronary intervention. Bourassa et al. (23) have shown that intentional incomplete revascularization in diabetic patients leads to excess mortality. Abaci et al. (24) also demonstrated that diabetic patients, while having a larger burden of coronary artery disease, had a much lower prevalence of collateral vessels. This would be expected to contribute to persistent myocardial ischemia and the increase in mortality rate. A report from the recent Arterial Revascularization Therapy Study (25) confirmed that diabetic patients with multivessel disease had lower event-free survival when treated with coronary stenting. In addition to all of these factors, women have also been shown to have smaller coronary arteries, which may in turn predispose to worse PCI outcomes (26). Taken together, the above findings suggest that diabetes and female sex in combination may present unique challenges to the performance of a successful procedure. Our results do not, however, suggest that diabetic women should not undergo percutaneous coronary intervention; rather, they indicate that diabetes may be an especially important adverse prognostic factor in women undergoing this procedure.

There are limitations to this study. Patients are registered in APPROACH at the time of cardiac catheterization. Thus, the results of this study may not reflect the outcomes of patients who are not referred for

Table 2—*Hazard ratios for total mortality associated with diabetes for up to 4 years*

	n	Crude HR* (95% CI)	Adjusted HR† (95% CI)
General IHD cohort*			
Men	13,152	1.92 (1.68–2.18)	1.25 (1.10–1.43)
Women	4,249	1.89 (1.57–2.78)	1.34 (1.11–1.62)

*$P = 0.92$ for sex comparison; †$P = 0.44$ for sex comparison. HR, hazard ratio; IHD, ischemic heart disease.

Table 3—*Hazard ratios for total mortality associated with diabetes in patient subgroups*

	n	Crude HR (95% CI)	Adjusted HR (95% CI)	*P**
MI Subgroup*				0.541
Men	4,135	1.79 (1.42–2.24)	1.03 (0.82–1.29)	—
Women	1,295	1.97 (1.45–2.68)	1.20 (0.88–1.63)	—
Subgroup without MI*				0.552
Men	9,017	1.91 (1.63–2.24)	1.39 (1.18–1.63)	—
Women	2,954	1.83 (1.45–2.31)	1.43 (1.13–1.81)	—
Treatment with CABG*				0.796
Men	3,203	1.77 (1.32–2.35)	1.23 (0.92–1.65)	—
Women	784	1.67 (1.09–2.55)	1.32 (0.86–2.01)	—
Treatment with PCI*				0.714
Men	5,022	1.82 (1.38–2.39)	1.28 (0.97–1.68)	—
Women	1,698	2.01 (1.36–2.97)	1.40 (0.94–2.06)	—
Treatment with medical therapy*				0.817
Men	4,924	1.90 (1.60–2.25)	1.26 (1.06–1.50)	—
Women	1,767	1.81 (1.42–2.30)	1.31 (1.02–1.67)	—

**P* for sex comparison of adjusted hazard ratios. CABG, coronary artery bypass graft; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.

investigation, and there is the potential for referral bias in our study findings. Second, we do not have detailed data on the specific treatment and adequacy of glycemic control in our patients with diabetes. Third, while suggestive of at least a slight sex difference in prognosis associated with diabetes, our epidemiological findings do not shed any light on the possible pathophysiological mechanisms underlying such a difference. A final important consideration is the influence of factors that are based on gender (i.e., how a person is responded to by social institutions like the health care system on the basis of the individual's gender presentation [27]); indeed, there are data to suggest that women are less likely to be referred for invasive cardiovascular investigations than men (28). The complex and interrelated contributions of social, sociological, and psychological factors that may contribute to outcomes in cardiovascular disease are difficult to fully characterize (29).

Despite these limitations, however, our study does provide useful information and advances our understanding of the relationship between patient sex and diabetes as a prognostic factor. Compared with previous studies, the present analysis of the APPROACH database finds only a slight, but consistent, sex difference in the prognostic importance of diabetes that may be of clinical relevance. This difference between sexes persists in subgroup analyses, and reveals that diabetes may be a particularly important adverse prognostic factor in women with acute myocardial infarction and in women treated with percutaneous coronary intervention. Further study is now required to determine whether diabetes and ischemic heart disease have unique pathophysiological features in women versus men, and to determine how recent innovations in the treatment of diabetic patients, such as intensive therapy, may modify these relationships over time.

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