Recent Trends in Cardiovascular Complications Among Men and Women With and Without Diabetes

GILLIAN L. BOOTH, MD, MSC[1,2,3]
MOIRA K. KAPRAL, MD, MSC[1,3,4,5]
KINWAH FUNG, MSC[3]
JACK V. TU, MD, PHD[1,3,6]

OBJECTIVE — To compare recent trends in cardiovascular disease (CVD) outcomes among men and women with diabetes with those in the nondiabetic population.

RESEARCH DESIGN AND METHODS — We conducted a retrospective cohort study using provincial health claims data to identify adults with (n = 670,602) and without (n = 9,190,721) diabetes living in Ontario, Canada, between 1 April 1992 and 31 March 2000. We compared changes in the annual age-/sex-adjusted rates and numbers of subjects admitted for acute myocardial infarction (AMI) and stroke and of deaths from AMI, stroke, and all causes between those with and without diabetes.

RESULTS — Over the 8-year period, the rate of patients admitted for AMI and stroke fell to a greater extent in the diabetic than the nondiabetic population (AMI: −15.1 vs. −9.1%, $P <$ 0.0001; stroke: −24.2 vs. 19.4%, $P <$ 0.0001). Diabetic patients experienced similar reductions in case-fatality rates related to AMI and stroke than those without diabetes (−44.1 vs. −33.2%, P = 0.1; −17.1 vs. −16.6%, P = 0.9, respectively). Declines in all-cause mortality were also comparable in the two populations. Over the same period, the number of diabetes cases increased from 405,471 to 670,602. Thus, while CVD rates fell, the number of events occurring in this population rose substantially (AMI: +44.6%, stroke: +26.1%, AMI deaths: +17.2%, and stroke deaths: +13.2%).

CONCLUSIONS — Our findings demonstrate a significant reduction in the rate of people affected by CVD within the diabetic population. However, as the number of people with diabetes rises, so may the absolute burden of CVD in our society.

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Diabetes is a serious and growing health problem. In 2002, the number of people with diabetes living in the U.S. was estimated to be 18.2 million (1). These values are projected to double over the next 2 decades based on the aging of the population and growing rates of obesity. Diabetes is associated with a two- to fourfold increase in the incidence of cardiovascular disease (CVD) and an elevated risk of premature death (2–4). As a consequence of the rising prevalence of diabetes, an increasing proportion of deaths from cardiovascular causes may be attributed to this condition (5).

In the U.S., mortality from coronary heart disease has dramatically fallen since the 1970s, with recent declines averaging ~3% per year (6–9). Earlier data suggest that improved heart disease outcomes were not equally shared between the diabetic and nondiabetic populations. Among participants in the first National Health and Nutritional Examination Survey, followed from 1971 to 1993, there was a lesser nonsignificant decline in coronary heart disease deaths among diabetic men compared with nondiabetic men and a trend toward rising mortality among diabetic women (10). A population-based study (5) conducted in Rochester, Minnesota, over the same time period yielded similar results. While a significant fall in overall mortality was observed among diabetic men, the temporal decline remained substantially less for men without diabetes. In contrast, a recent analysis from the Framingham Heart Study observed a 50% lower rate of incident CVD events among both diabetic and nondiabetic cohorts who were followed after 1977 compared with those examined in the 1950s and 1960s (11).

The last decade has seen tremendous advances in the treatment of heart disease and CVD risk factors. Thus, earlier observations may not necessarily reflect current patterns of morbidity and mortality. To evaluate the impact of diabetes on recent trends in cardiovascular outcomes, we conducted a population-based study using comprehensive health claims data in Ontario, Canada, between the years 1992 and 2000.

RESEARCH DESIGN AND METHODS

— The Registered Persons Database was used to identify all residents of Ontario aged ≥20 years who were alive and eligible for coverage under the Ontario Health Insurance Plan during each fiscal year from 1992 (1 April 1992 to 31 March 1993) to 1999 (1 April 1999 to 31 March 2000). As in other Canadian provinces, hospital, laboratory, and physician services are universally funded through a single-payer system administered through the Ontario government; therefore, these data sources include records for virtually all residents in the province. The Registered Persons Database includes vital statistic information based on death certificates collected by the Office of the Registrar General. Because the Registered

From the [1]Department of Medicine, University of Toronto, Toronto, Ontario, Canada; the [2]Division of Endocrinology and Metabolism, St. Michael's Hospital, Toronto, Ontario, Canada; the [3]Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada; the [4]Department of Medicine, University Health Network, Toronto, Ontario, Canada; the [5]University Health Network Women's Health Program, Toronto, Ontario, Canada; and the [6]Department of Medicine, Sunnybrook and Women's College Health Sciences Centre, Toronto, Ontario, Canada.

Address correspondence and reprint requests to Dr. Gillian L. Booth, Division of Endocrinology and Metabolism, St. Michael's Hospital, 61 Queen St., East, 6-147, Toronto, Ontario, Canada M5C 2T2. E-mail: boothg@smh.toronto.on.ca.

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Abbreviations: AMI, acute myocardial infarction; CVD, cardiovascular disease; ODD, Ontario Diabetes Database.

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

Persons Database may underreport deaths to a small extent, we excluded individuals aged ≥65 years whose last date of contact with the health care system or last prescription filled through Ontario's Drug Benefit Program was >90 days before the start of the fiscal year (<1% of the total eligible population). The final study population was 9,164,603 in fiscal 1992 and 9,861,323 in fiscal 1999.

Classification of diabetes

Diabetes status was assigned to each individual in order to create yearly diabetic and nondiabetic cohorts. To do so, we used the Ontario Diabetes Database (ODD), a provincial registry that uses administrative health claims from hospitalizations and ambulatory services to identify individuals with diagnosed diabetes (12). Any individuals having at least one hospitalization or two physicians' service claims bearing a diagnosis of diabetes (ICD-9/diagnostic code 250.x) within a 2-year period are included in the ODD. Once cases enter the database, they remain there until a record of their death or migration out of province occurs, regardless of their subsequent health care utilization. This algorithm was associated with an 86% sensitivity and 98% specificity for identifying patients in whom diabetes was recorded in primary care charts (12). The ODD does not discriminate between cases of type 1 and type 2 diabetes.

Based on the above algorithm, some individuals diagnosed with diabetes in a given year might not fulfill the criteria for entering the ODD until the subsequent 1–2 years. For this reason, in our main analysis we classified individuals as having diabetes within a given fiscal year if they had a record in the ODD during the same year or the subsequent 2 years. As a sensitivity analysis, the diabetic cohort was restricted to only those individuals with records in the ODD during a specific year. With either method, the nondiabetic comparison group consisted of individuals who did not have records in the ODD during any period from which we had available data. Analyses involving in-hospital deaths used a different algorithm: diabetes status was ascertained at the time of discharge so that those who died during their hospital stay had an equal opportunity to enter the ODD as those who survived.

CVD outcomes

The following end points were evaluated: acute myocardial infarction (AMI), stroke, and death from AMI, stroke, and all causes. Admissions for AMI were detected from hospitalization records listing an ICD-9 code of 410.x as the most responsible diagnosis using a previously validated algorithm (13). To do so, admissions where the length of stay was <3 days were excluded, unless the episode involved transfer to another acute care hospital or the patient died within the first 3 days of hospital admission. Stroke admissions were detected from hospitalization records listing an ischemic or hemorrhagic stroke as the most responsible diagnosis (ICD-9 codes 431, 434, and 436). In-hospital deaths were identified from hospital discharge abstracts and other deaths from the Registered Persons Database. Disease-specific mortality and deaths occurring out of province could not be obtained from these or other sources. Records for individual persons were linked across data sets using a unique anonymous identifier, thus retaining confidentiality.

Analysis

We examined the impact of diabetes status on changes in age-/sex-adjusted rates and the numbers of affected individuals admitted for AMI and stroke during fiscal years 1992–1999. Rates were calculated using the total number of individuals who experienced an outcome within a given year as the numerator and the total number of individuals in the cohort during the same time period as the denominator. Only the first event in a given year contributed to each rate. Age and sex adjustment were performed using the direct method standardized to the nondiabetic population. Multiple linear regression was used to determine the impact of the following covariates on each outcome: diabetes status, year, and the interaction between diabetes status and year. This analysis was repeated for subgroups defined by age (<65 years vs. ≥65 years) and sex. Changes in rates and the number of deaths from AMI, stroke, and all causes were evaluated using similar methods. All analyses were conducted using SAS 8.2. This protocol received ethical approval from the institutional review board at Sunnybrook and Women's College Health Sciences Centre.

RESULTS

Between fiscal years 1992 and 1999, there were 151,872 patients admitted to the hospital for an AMI, 107,963 patients admitted for stroke, and 602,187 deaths from any cause. Table 1 lists yearly age-/sex-adjusted rates of all end points by diabetes status. After adjustment for age and sex, individuals with diabetes were over three times more likely to be admitted for AMI or stroke and 1.6 times more likely to die from one of these outcomes than those without diabetes.

Temporal changes in CVD rates

Over the 8-year observation period, the diabetic population experienced a greater proportional reduction in age-/sex-adjusted rates of patients admitted for AMI and stroke than those without diabetes (Table 1). For AMI admissions, this finding was restricted to men and women aged <65 years (diabetes versus no diabetes: −18.8 vs. −15.9%, $P < 0.0001$ and −28.4 vs. −13.9%, $P = 0.0004$, respectively) (Fig. 1). In contrast, changes over time were markedly attenuated in older groups, amounting to only a 7.6 and 5.4% reduction in those with and without diabetes ($P = 0.05$ for the diabetes-year interaction). Trends in the rate of patients admitted for stroke did not vary by age. When we excluded very new cases from our yearly diabetic cohorts, the overall event rates were higher and the proportional fall in rates over time were greater in this population (data not shown).

Overall, individuals with diabetes experienced similar reductions in age-/sex-adjusted rates of mortality from AMI, stroke, and all causes as those without this disease. With respect to AMI-related deaths, improvements in rates over time were less favorable among older subsets of the population (aged ≥65 years: −24.5 vs. −24.4%, $P = 0.5$; aged <65 years: −57.9 vs. −44.6%, $P = 0.1$, in diabetic versus nondiabetic groups, respectively). In contrast, changes in in-hospital mortality from stroke were of a similar magnitude in younger and older patients; however, trends over time were only statistically significant in the latter. There was considerable variation in case fatality rates from year to year in younger groups, likely owing to the relatively fewer deaths in this population.

Temporal changes in numbers of individuals affected by CVD

Between fiscal years 1992 and 1999, the number of individuals with diabetes in our cohort increased by 65.4%, from 405,471 to 670,602. Because of this dramatic growth in the number of diabetes cases, the number of cardiovascular events in this population also rose, albeit to a lesser extent, resulting in a net reduc-

Table 1—*Rates of individuals affected by CVD by fiscal year*

	Age/sex-adjusted rates*								Change in rate		
Outcome/subgroup	1992	1993	1994	1995	1996	1997	1998	1999	%†	*P* value for trend‡	*P* value diabetes vs. no diabetes§
AMI											
Diabetes	658.8	625.0	610.0	590.2	600.6	580.0	552.7	554.4	−15.1	0.0002	<0.0001
No diabetes	198.1	191.8	187.0	185.8	189.5	182.5	178.9	178.1	−9.1	0.0009	
In-hospital mortality after AMI											
Diabetes	9,917.7	10,912.0	7,854.6	6,340.5	6,969.1	6,621.6	5,962.3	6,486.4	−44.1	0.01	0.1
No diabetes	6,055.0	7,079.3	4,851.2	5,367.1	4,692.9	4,602.9	4,805.7	4,317.7	−33.2	0.02	
Stroke											
Diabetes	419.5	413.9	393.3	384.5	373.3	353.3	333.3	319.0	−24.2	<0.0001	<0.0001
No diabetes	149.1	152.8	148.4	142.0	140.1	134.5	126.5	122.7	−19.4	0.0001	
In-hospital mortality after stroke											
Diabetes	13,498.7	9,812.6	18,348.4	9,015.2	15,157.0	16,687.4	8,348.1	10,319.4	−17.1	0.6‖	0.9
No diabetes	13,920.3	11,807.6	12,396.7	10,048.2	9,558.7	12,207.4	10,901.2	11,151.7	−16.7	0.2‖	
All-cause mortality											
Diabetes	1,452.1	1,522.0	1,507.1	1,466.1	1,443.0	1,410.7	1,342.0	1,336.3	−11.1	0.006	0.7
No diabetes	934.1	941.8	909.5	890.2	881.3	853.9	806.1	799.0	−15.8	<0.0001	

*Rates = number of people affected per 100,000 population. †Percent change in rates over the 8-year period was estimated from line of best fit. ‡*P* values for trends based on the β coefficient (slope) from linear regression models. §*P* value for diabetes vs. no diabetes is based on the interaction between diabetes status and fiscal year from multiple linear regression models. ‖*P* value for trend <0.001 only for age-group ≥65 and older.

tion in admission rates over time (Fig. 2). However, the magnitude by which the number of diabetic individuals experiencing an AMI or stroke increased far exceeded that of the nondiabetic population (% change in the number of AMIs: +44.6 vs. +9.2%, $P = 0.0005$; % change in the number of strokes: +26.1 vs. −4.2%, $P = 0.0004$). The annual number of deaths from AMI and stroke also increased in those with diabetes but declined among those without this disease (% change in the number of AMI deaths: +17.2 vs. −11.9%, $P = 0.0006$; % change in the number of stroke deaths: +13.2 vs. −19.9%, $P < 0.0001$). By 1999, over one-third of cardiovascular events and nearly one-quarter of all deaths occurred in the diabetic population.

CONCLUSIONS — Our analysis indicates a substantial decline in cardiovascular event rates among residents of Ontario, Canada, between 1992 and 2000. Men and women with diabetes experienced a greater proportional reduction in rates of admission for AMI and stroke compared with the nondiabetic population and similar declines in cardiovascular and all-cause mortality. This study included virtually all adults in the general population and therefore reflects outcomes as they exist in the real world. Our findings suggest that the care and management of patients with diabetes has genuinely improved in recent years and point to the contribution of both primary and secondary prevention strategies in affecting these changes.

Our data are supported by previous observations indicating a decline in coronary heart disease mortality within the general U.S. population (6–9). Similar improvements in survival following AMI were noted in Ontario during the 1980s (14). Our findings demonstrate further reductions in post-AMI mortality in subsequent years, likely incurred by recent advances in the management of acute coronary events. Favorable trends in the prevalence of hypertension, hypercholesterolemia, and cigarette smoking may also have contributed to overall declines in vascular disease (15–18). There is now an unprecedented body of evidence supporting the use of ACE inhibitors, antihypertensive medications, and lipid-lowering agents for both primary and secondary prevention of CVD events in high-risk populations, including those with diabetes (19–21). Recent data from Ontario's Drug Benefit Program showed a parallel rise in the use of cardioprotective agents among elderly people with diabetes, which may have contributed to the improved outcomes observed in this population (22).

Our findings demonstrate similarly favorable reductions in mortality related to AMI and stroke throughout the 1990s among patients with diabetes. This observation differs from earlier cohort studies from the U.S. demonstrating a lesser decline in heart disease mortality among those with diabetes compared with the nondiabetic population but is supported by more recent data based on discharge records from the Veterans Affairs medical system (5,10,23). A possible explanation for these discrepancies is that improved outcomes in the diabetic population are a recent phenomenon. Physicians may have been slower to adopt new therapies in complex patients, such as those with diabetes, causing outcomes in this group to lag behind other segments of the population. Evidence for this is seen in the setting of AMI, where diabetic patients are less likely than similar patients without diabetes to receive thrombolysis, aspirin, or β-blockers or to be referred for revascularization (24–28). The importance of diabetes as a major cardiovascular risk factor has received considerable attention over the last decade. This fact alone might have initiated more aggressive use of car-

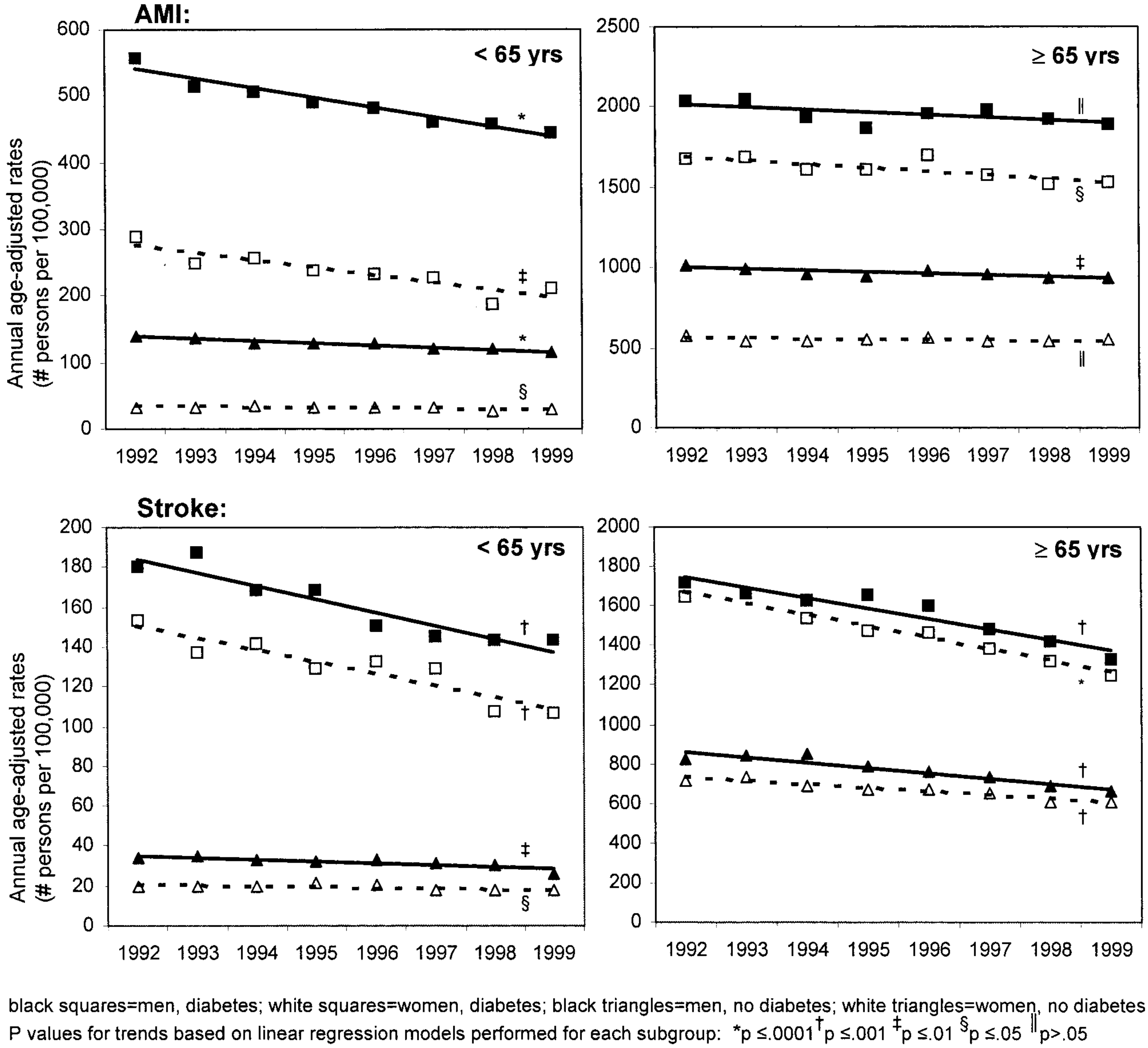

Figure 1—*Trends in age-adjusted rates of patients admitted for AMI and stroke by age and sex.*

dioprotective therapies in patients with diabetes, irrespective of their coronary status. Before this time, most studies that focused on cardiovascular risk reduction included insufficient numbers of diabetic subjects to demonstrate a clear benefit in this subgroup. Thus, the lack of proven efficacy in patients with diabetes may have deterred some physicians from using these therapies in the past.

The elderly are another group often excluded from randomized controlled trials. We found that trends in rates of admission and case-fatality from AMI were less favorable in those aged ≥65 years than in younger individuals. Other studies in the literature support this finding (5,10,13). The intensity with which primary and secondary prevention strategies are applied appears to be less in older groups, (29–31) despite evidence from clinical trials suggesting that cardioprotective agents confer a similar degree of benefit in high-risk patients of all ages (21,32,33). Thus, the gap between best evidence and actual practice may be substantially greater in the elderly, explaining the observed disparity in the benefit gained over time between older and younger subsets of the population.

Our work shows a substantial fall in rates of hospitalization for CVD over the last decade, despite the introduction of more sensitive laboratory tests to diagnose AMI. In contrast, several U.S. studies failed to identify a decline in overall rates of myocardial infarction, despite obvious reductions in post-AMI mortality (8,9, 34). Again, differences in the years that were studied could account for some of these discrepancies. However our analysis was also stratified on the basis of diabetes status, while many others were not. Given the heightened risk of CVD within the diabetic population, the rising prevalence of diabetes itself may lead to increases in the overall rate of admissions, despite actual decreases in rates within individuals at risk. Therefore, failure to account for the changing burden of diabetes within the AMI population could explain why these rates appeared unchanged in some of these previous studies.

There are several limitations to our

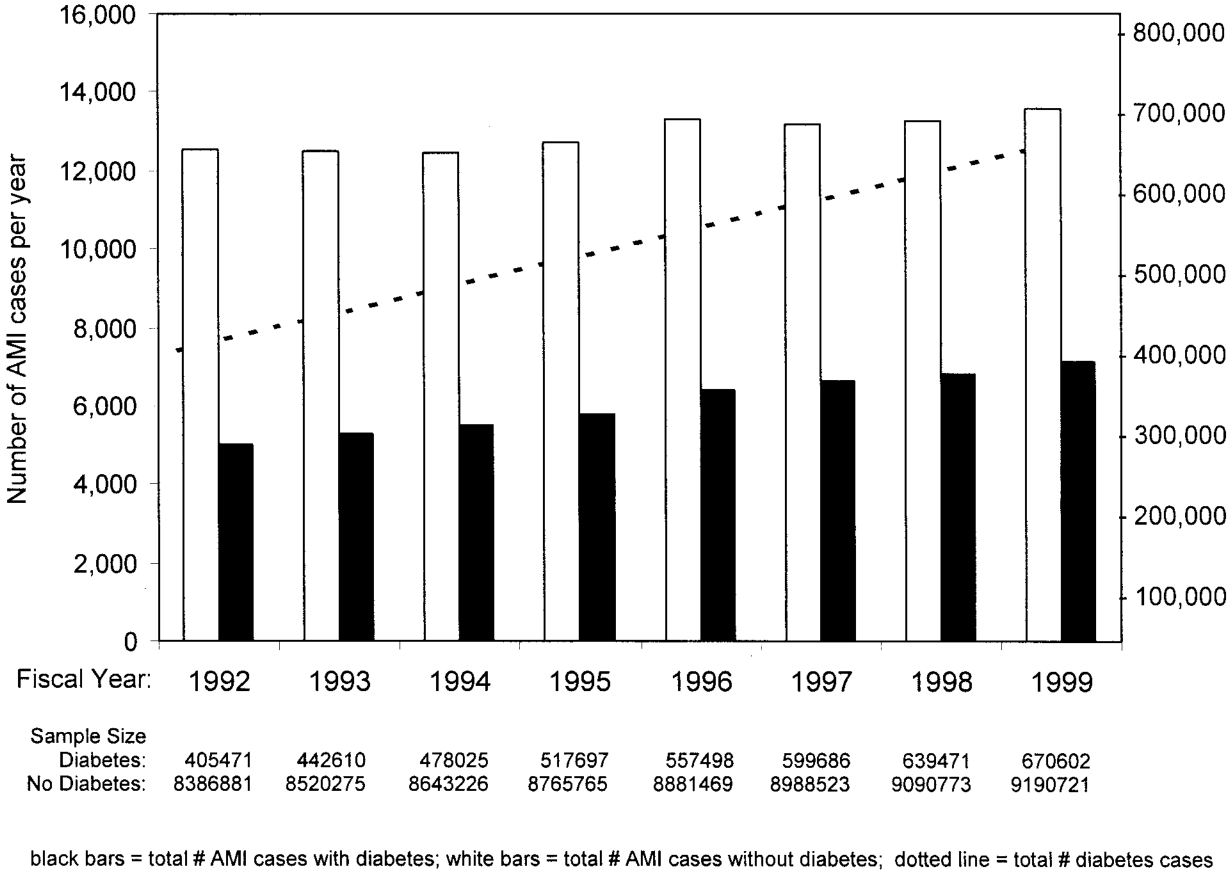

Figure 2—*Number of AMI and diabetes cases per year.*

analysis that merit discussion. First, increased ascertainment of diabetes cases over time could have influenced the rate at which complications fell. However, when using a broad definition of diabetes that captured more newly diagnosed cases, we observed a lesser decline in CVD rates than when excluding such cases, thereby minimizing the apparent difference in rates between the diabetic and nondiabetic populations. Second, systematic differences in how cardiovascular events were identified over time might also have contributed to our findings. Our algorithm excluded short-stay survivors who were presumably admitted to rule out an AMI. While lengths of stay for AMI admissions in Canada have declined over time, changes between 1994 and 2000 were modest and not significant in previous analyses (35). Last, while our findings demonstrate a substantial fall in CVD rates, we cannot ascribe this change to one particular intervention over another.

Our findings showed a substantial fall in cardiovascular event rates among men and women with diabetes between 1992 and 2000. Further improvements in cardiovascular outcomes are possible with more aggressive risk reduction in this population. However, while the risk to individual patients may fall, the absolute number of people with CVD is expected to rise, given the dramatic growth of diabetes in the population. In Ontario alone, the prevalence of diabetes rose 31% between 1994 and 1999 (12). Moreover, projections estimate that the number of people affected by diabetes in the U.S. and Canada will double in the next 20 years. Failure to address the impending diabetes epidemic may result in a concomitant escalation in overall rates of CVD as well as the number of affected individuals in the population. A greater focus on preventing diabetes will be necessary to avoid this inexorable rise in the burden of CVD on our health care systems and on society.

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