

## Sex Differences in Outcomes after Stroke in Patients with Diabetes in Ontario, Canada

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*Background:* Outcomes after stroke in those with diabetes are not well characterized, especially by sex and age. We sought to calculate the sex- and age-specific risk of cardiovascular outcomes after ischemic stroke among those with diabetes. *Methods:* Using population-based demographic and administrative health-care databases in Ontario, Canada, all patients with diabetes hospitalized with index ischemic stroke between April 1, 2002, and March 31, 2012, were followed for death, stroke, and myocardial infarction (MI). The Kaplan–Meier survival analysis and Fine–Gray competing risk models estimated hazards of outcomes by sex and age, unadjusted and adjusted for demographics and vascular risk factors. *Results:* Among 25,495 diabetic patients with index ischemic stroke, the incidence of death was higher in women than in men (14.08 per 100 person-years [95% confidence interval [CI], 13.73–14.44] versus 11.89 [11.60–12.19]) but was lower after adjustment for age and other risk factors (adjusted hazard ratio [HR], .95 [.92–.99]). Recurrent stroke incidence was similar by sex, but men were more likely to be readmitted for MI (1.99 per 100 person-years [1.89–2.10] versus 1.58 [1.49–1.68] among females). In multivariable models, females had a lower risk of readmission for any event (HR, .96 [95% CI, .93–.99]). *Conclusions:* In this large, population-based, retrospective study among diabetic patients with index stroke, women had a higher unadjusted death rate but lower unadjusted incidence of MI. In adjusted models, females had a lower death rate compared with males, although the increased risk of MI among males persisted. These findings confirm and quantify sex differences in outcomes after stroke in patients with diabetes. **Key Words:** Epidemiology—stroke—diabetes—gender differences—sex differences, mortality—outcomes.

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## Introduction

There are sex differences in the risk of cardiovascular disease in people with diabetes. Compared with men, women with diabetes have a 40% higher risk of incident coronary heart disease<sup>1</sup> and a 27% higher risk of stroke.<sup>2</sup> However, sex differences in outcomes in diabetic patients following an incident event are unclear, with conflicting findings in previous studies.<sup>3,4</sup> Sex differences have been demonstrated for myocardial infarction (MI)<sup>5,6</sup> and other cardiovascular diseases,<sup>7</sup> but data on sex differences in outcomes among people with diabetes after incident stroke are less consistent. Relatively small studies have reported higher in-hospital mortality<sup>8</sup> and long-term mortality<sup>9</sup> for diabetic females, but others have shown no association of sex and outcomes<sup>10,11</sup> Furthermore, prior studies mostly examined mortality and did not measure readmission rates. Studies to date have not adequately assessed for socioeconomic status and medication usage, which may confound the relationship between sex and outcomes. There is a lack of reliable population-based data on the effect of sex on mortality and readmissions among diabetic patients following an incident stroke.

The objective of this analysis was to examine differences in cardiovascular events and mortality by sex and age among those with diabetes after ischemic stroke in Ontario. We hypothesized that women had higher mortality compared with men and that the readmission risk for cardiovascular events differed by sex.

## Methods

We conducted a retrospective analysis of a population-based sample using linked administrative databases in Ontario, Canada's most populous province. Because of a government-funded health insurance for all permanent residents of Ontario, data were available on the entire population. The Ontario Registered Persons Database provided data on mortality after stroke, and the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) identified readmissions for stroke and MI. CIHI-DAD contains  $\leq 25$  diagnosis fields for admissions to Ontario hospitals and uses the International Classification of Diseases, 10th revision coding system (ICD-10) for the year 2002 onwards. In previous studies of CIHI-DAD in Canadian hospitals, there was a high positive predictive value (85% for ischemic stroke, 98% for intracerebral hemorrhage, and 91% for subarachnoid hemorrhage) and a Kappa of .89 for the agreement between the coder and the researcher using ICD-10 codes.<sup>12</sup> The Ontario Drug Benefits database provided information on prescriptions filled by all residents aged  $\geq 65$  years. These databases were linked via a unique, encoded identifier and analyzed at the Institute for Clinical Evaluative Sciences. The institutional ethics review board of the Sunnybrook Health Sciences Centre approved this study.

## Sample Selection

We included those with an index ischemic stroke admission during the study period in the CIHI-DAD, identified with any of the following ICD-10 codes: I63 (excluding I63.6), I64, H34.0, or H34.1 in the "most responsible diagnosis" field, which has been shown to have a 92% accuracy for stroke diagnosis.<sup>13</sup> We identified the diagnosis of diabetes prior to or at the time of the index ischemic stroke admission by linking to the Ontario Diabetes Database, which has a sensitivity of 91% and a specificity of 99%.<sup>14</sup> We limited the sample to those with ischemic stroke and diabetes who were  $\geq 18$  years of age at the time of admission. Index stroke admissions from April 1, 2002 to March 31, 2012, were included, with maximum follow-up until March 31, 2013.

## Baseline Assessment

Age was calculated as age at admission for the index ischemic stroke. Income was estimated using neighborhood-level household income and was categorized into quintiles. The duration of diabetes was calculated by using the diagnosis date in the Ontario Diabetes Database and was categorized into 0 to  $<3$ , 3 to  $<6$ , and  $\geq 6$  years. The duration of Ontario residence was inferred from the duration of having a health card and was categorized into: 0 to  $<5$ , 5 to  $<10$  and  $\geq 10$  years. Using standard ICD-9 (prior to 2002) and ICD-10 (2002 onwards) code clusters, we identified history of stroke or transient ischemic attack (TIA), atrial fibrillation, hypertension, MI, coronary artery disease (CAD), and peripheral vascular disease (PVD).

The Charlson Comorbidity Index (CCI) was calculated using all diagnosis codes and types from all hospitalizations during the 2-year period prior to and including the index admission using  $\leq 25$  available ICD-9 and ICD-10 codes for each hospitalization. As all participants in this analysis had diabetes, the diabetes indicators were excluded from our CCI calculation. The CCI was dichotomized into  $<2$  versus  $\geq 2$ , as in previous research.<sup>15</sup>

Only patients  $\geq 65$  years of age had complete information on prescription medication use. Baseline medication was defined as any prescription medication use within a 120-day window after the index stroke discharge, and medication classes included diabetic, statin, and antihypertensive medications as well as warfarin. Aspirin, which is available over the counter, had an incomplete capture; hence, antiplatelet medication use was not adjusted for in the sensitivity analyses.

## Longitudinal Follow-Up

Outcomes were death, any-cause readmission, stroke/TIA readmission, MI readmission, stroke or MI readmission, and a composite of death or any-cause readmission. To create these outcomes, hospital readmissions for the

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