Cardiovascular Disease in Patients With Schizophrenia in Saskatchewan, Canada

Suellen M. Curkendall, Ph.D.; Jingping Mo, M.D., Ph.D.; Dale B. Glasser, Ph.D.; Mary Rose Stang, Ph.D.; and Judith K. Jones, M.D., Ph.D.

Background: Studies have shown that patients with schizophrenia have higher rates of cardiovascular disease and mortality compared with the general population. However, population-based data on the prevalence, incidence, and mortality of cardiovascular disease are needed.

Method: In this retrospective cohort study, the Saskatchewan Health databases were searched for all patients diagnosed with schizophrenia (ICD-9 code 295) in 1994 or 1995. 3022 subjects were identified. For each subject, 4 age- and sex-matched comparison individuals were selected randomly among residents of the province who had no diagnosis of schizophrenia or any other mental disorders and who received no prescriptions for antipsychotic medications. Prevalence of cardiovascular morbidity during 1994 and 1995 and incidence of cardiovascular morbidity and mortality during the follow-up period of January 1996 through March 1999 were analyzed.

Results: Concerning prevalence of morbidity in schizophrenia patients, significantly increased risk-adjusted odds ratios were as follows: arrhythmia, 1.5 (95% CI = 1.2 to 1.8); syncope, 4.0 (95% CI = 2.0 to 7.9); heart failure, 1.7 (95% CI = 1.4 to 2.2); stroke, 2.1 (95% CI = 1.6 to 2.7); transient cerebral ischemia, 2.6 (95% CI = 1.7 to 3.7); and diabetes, 2.1 (95% CI = 1.8 to 2.4). Odds of acute myocardial infarction, ischemic heart disease, and ventricular arrhythmias were not significantly different from those for the comparison group. Concerning incidence of morbidity and mortality in the patients, adjusted relative risk was significantly increased for ventricular arrhythmia, 2.3 (95% CI = 1.2 to 4.3); heart failure, 1.6 (95% CI = 1.2 to 2.0); stroke, 1.5 (95% CI = 1.2 to 2.0); diabetes, 1.8 (95% CI = 1.2 to 2.6); all-cause mortality, 2.8 (95% CI = 2.3 to 3.4); and cardiovascular mortality, 2.2 (95% CI = 1.7 to 2.8).

Conclusions: Persons with schizophrenia appear to be at greater risk for cardiovascular morbidity and mortality than those in the general population.

(J Clin Psychiatry 2004;65:715–720)

Received July 14, 2003; accepted Nov. 4, 2003. From Healthcare Data Analysis, Vienna, Va. (Dr. Curkendall); Global Epidemiology (Dr. Mo) and U.S. Sexual Health Team (Dr. Glasser), Pfizer Inc, New York, N.Y.; Population Health Branch, Saskatchewan Health, Regina, Saskatchewan, Canada (Dr. Stang); and The Degge Group, Ltd., Arlington, Va. (Dr. Jones). Dr. Curkendall was formerly with The Degge Group, Ltd.

Supported by Pfizer Inc, New York, N.Y.

Some of the results of this study were presented in poster form at the 154th annual meeting of the American Psychiatric Association, May 5–10, 2001, New Orleans, La.; the 41st meeting of the New Clinical Drug Evaluation Unit, May 28–31, 2001, Phoenix, Ariz; and the 7th World Congress of Biological Psychiatry, July 1–6, 2001, Berlin, Germany.

This study is based in part on de-identified data provided by the Saskatchewan Department of Health. The interpretation and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Department of Health.

Corresponding author and reprints: Suellen M. Curkendall, Ph.D., 220 Lawyers Rd., NW, Vienna, VA 22180 (e-mail: Suellen.Curkendall@cox.net).

Previous studies suggest that patients with schizophrenia have a significantly increased burden of cardiovascular disease and diabetes[1,2] and that cardiovascular mortality contributes to the excess mortality in persons with schizophrenia.[3–6] However, recent population-based data are lacking on the prevalence and incidence of and mortality from cardiovascular disease among patients with schizophrenia. Most studies on mortality were conducted among patients with schizophrenia prior to 1992[5,7,8] and thus before the widespread use of atypical antipsychotic medications. In addition, the majority of the studies were conducted in inpatient settings[6–8] and did not include outpatients with schizophrenia, so they are not reflective of the overall population with schizophrenia. Population-based health service databases in Saskatchewan, Canada, enable the study of exposures and outcomes in a defined geographic population of about 1 million residents. The objectives of the present study were to estimate the prevalence, incidence, and mortality of cardiovascular outcomes among patients with schizophrenia and to evaluate whether these patients have higher prevalence and incidence of and mortality from cardiovascular disease than the general population.

METHOD

Data Source

The Province of Saskatchewan, Canada, provides medical benefits to all residents of Saskatchewan, a

Table 1. Cardiovascular Outcome and Mortality Definitions

Outcome	Definition Code
AMI	AMI diagnosis ICD-9 410
Non-AMI ischemic heart disease	Ischemic heart disease ICD-9 411, 414 Old myocardial infarction ICD-9 412 Angina pectoris ICD-9 413
Arrhythmia	Arrhythmia diagnoses ICD-9 426–427 Arrhythmia medications Pacemaker implants and procedures
Ventricular arrhythmia	Ventricular tachycardia ICD-9 427.1 Ventricular fibrillation and flutter ICD-9 427.4 Cardiac arrest ICD-9 427.5
Syncope	Syncope diagnosis ICD-9 780.2
Heart failure	Congestive or unspecified heart failure ICD-9 428
Stroke	Intracerebral hemorrhage ICD-9 431 Intracranial hemorrhage ICD-9 432 Occlusion and stenosis of precerebral arteries ICD-9 433 Occlusion of cerebral arteries ICD-9 434 Acute but ill-defined cerebrovascular disease ICD-9 436
Transient cerebral ischemia	Transient cerebral ischemia diagnosis ICD-9 435
Diabetes	Diabetes diagnosis ICD-9 250 Oral antidiabetic medications Insulin
All-cause mortality	Any death
Suicide	Death in which suicide is listed as a contributing cause
Sudden death	Death in which sudden death ICD-9 798 is listed as a contributing cause
Cardiovascular mortality	Death in which any cardiovascular condition is listed as a contributing cause

Abbreviation: AMI = acute myocardial infarction.

population of about 1 million people. As universal coverage of health insurance is provided in Saskatchewan, there is no eligibility distinction based on socioeconomic status. Saskatchewan Health, a provincial government department, therefore maintains administrative longitudinal health services databases.[9] The centralized database includes health insurance registration data, physician claims, hospital separations, outpatient prescription drug records, and vital statistics, including the date and cause of deaths registered in Saskatchewan. One underlying cause of death and up to 13 contributing causes of death that are recorded on the death certificate are reported in the vital statistics database.

The Saskatchewan data have been widely used in epidemiologic studies and are particularly suited to the study of patients with schizophrenia because patients can be followed in the databases as long as they are residents and eligible for benefits. An additional strength is the lack of socioeconomic bias in eligibility for services. It has been shown that schizophrenia diagnoses are recorded reliably in the Saskatchewan Health databases.[10] One limitation is that not all diagnoses made in psychiatrists' offices are recorded in the databases because approximately half of the psychiatrists in Saskatchewan are salaried and are not required to submit fee-for-service medical claims. The Saskatchewan data have been validated for the recording of ischemic heart disease, including acute myocardial infarction.[11]

All individuals, excluding registered Indians (because their drug records are not included in the databases), 18 years or older as of January 1, 1994, were eligible for this study. A search of the Saskatchewan Health databases identified 3022 persons who had been diagnosed with schizophrenia, ICD-9 code 295, at a physician's office or in the hospital in 1994 or 1995. For each patient with schizophrenia, 4 age- and sex-matched comparison individuals were selected randomly among individuals who had no diagnosis of schizophrenia or any other mental disorders (ICD-9 codes 290–319) and who received no prescriptions for antipsychotic medications.

Outcomes

Prevalence and incidence of cardiovascular outcomes and mortality were compared between patients with schizophrenia and the matched comparison group. The outcomes were defined using ICD-9 diagnostic codes, procedures, and prescriptions for particular drugs (Table 1). Patients who died and had more than 1 contributing cause of death were assigned 1 cause according to the following hierarchy: suicide, sudden death, and death with (other) cardiovascular contributing causes.

Analyses

Odds ratios for comparing prevalence of cardiovascular outcomes in persons with schizophrenia and their matched comparison group were computed for the period 1994 through 1995. Risk ratios comparing incidence were computed for the period January 1996 through March 1999. Both patients with schizophrenia and matched individuals who were free of the specific cardiovascular outcome during the prevalence study period were followed up from January 1996 through March 1999 to identify incidence cases of that particular cardiovascular outcome.

Multivariate analyses were conducted to compute odds ratios of prevalence and risk ratios of incidence (with 95% confidence intervals) for each outcome in the schizophrenia group compared with the nonschizophrenia group. Logistic regression was used to compute odds ratios, and Poisson regression was used to compute risk ratios. The risk factors included in the models were age group, sex, history of cardiovascular disease, hypertension, hyperlipidemia, diabetes, and serious pulmonary disease (Table 2 shows definitions for these risk factors). Not all risk factors were adjusted for all outcomes (e.g., diabetes was not used as a risk factor for diabetes). To avoid overspecification and facilitate model convergence, selected risk factors were removed from some models (see Tables 5 and 6).

Table 2. Cardiovascular Risk Factor Definitions

Risk Factor	Definition Code
Hypertension	Essential hypertension ICD-9 401
	Hypertensive heart disease ICD-9 402
	Hypertensive renal disease ICD-9 403
	Hypertensive heart and renal disease ICD-9 404
	Secondary hypertension ICD-9 405
Hyperlipidemia	Disorders of lipid metabolism ICD-9 272
	Antilipemic medications
Diabetes	Diabetes diagnosis ICD-9 250
	Oral antidiabetic medications
	Insulin
Serious pulmonary disease	Bronchitis ICD-9 490, 491
	Emphysema ICD-9 492
	Bronchiectasis ICD-9 494
	Chronic airways obstruction ICD-9 496
	Empyema ICD-9 510
	Surgical procedures on the lung
Prior cardiovascular disease	Cardiovascular malfunction arising from mental factors ICD-9 306.2
	Ischemic heart disease ICD-9 411, 414
	Old myocardial infarction ICD-9 412
	Angina pectoris ICD-9 413
	Acute myocarditis ICD-9 422
	Cardiomyopathy ICD-9 425
	Heart failure ICD-9 428
	Ill-defined heart disease ICD-9 429
	Rheumatic fever with heart involvement ICD-9 391
	Chronic rheumatic heart disease ICD-9 393–398
	Endocarditis and other endocardium disease ICD-9 421, 424
	Pericarditis ICD-9 420, 423

Table 3. Baseline Characteristics of Patients With Schizophrenia and Their Matched General Population Comparison Group in Saskatchewan, Canada, 1994–1995[a]

Characteristic	Patients With Schizophrenia (N = 3022)	Sample of General Population Matched to Patients With Schizophrenia (N = 12,088)
Age, y		
Mean (SD)	49.6 (17.8)	49.6 (17.7)
Median	47	47
Male	49.5	49.5
Comorbidities		
Hypertension	13.7	16.7
Hyperlipidemia	5.4	6.3
Cardiovascular disease	10.6	8.7
Serious pulmonary disease	16.1	10.3
Cardiovascular medication usage		
Antiarrhythmic agents	0.1	0.4
ACE inhibitors	7.3	7.6
Calcium channel blockers	5.4	5.8
Beta blockers	5.8	5.1
Combination beta blockers	0.3	0.6
Diuretics for hypertension	9.5	9.0
Other hypotensive agents	1.9	1.7
Other diuretics for heart disorders	6.8	4.6
Antianginal agents	3.1	3.5
Anticoagulants	1.4	1.5
Antiplatelet agents	0.1	0.1
Antilipemics	2.0	3.0
Digoxin	2.8	2.5

[a]Values shown as percentages unless otherwise specified.
Abbreviation: ACE = angiotensin converting enzyme.

RESULTS

Half of the patients with schizophrenia were men and half were women (Table 3). The median age of patients with schizophrenia was 47 years; for women, 53 years, and for men, 43 years. The patients were more likely to have a history of cardiovascular disease (10.6% vs. 8.7%) and serious pulmonary disease (16.1% vs. 10.3%) than the population comparison group at baseline. The proportion of patients who had prescriptions for cardiovascular medications was similar in the 2 groups except that diuretics for cardiovascular disease (bumetanide, ethacrynic acid, or furosemide) were used more frequently among the patients with schizophrenia (6.8% compared with 4.6%). During the entire study period (January 1994 to March 1999), 86.9% of the patients had at least 1 prescription for an antipsychotic medication, including 62.3% who had a prescription for a phenothiazine, 30.5% who had a prescription for haloperidol, and 32.3% who had a prescription for a novel agent, mainly risperidone (27.8%) (Table 4).

The prevalence of most of the cardiovascular conditions of interest was higher among the schizophrenia group than among the comparison group (Table 5). Adjusted odds ratios for arrhythmias (OR = 1.5, 95% CI = 1.2 to 1.8), syncope (OR = 4.0, 95% CI = 2.0 to 7.9), heart failure (OR = 1.7, 95% CI = 1.4 to 2.2), stroke (OR = 2.1, 95% CI = 1.6 to 2.7), transient cerebral ischemia (TCI) (OR = 2.6, 95% CI = 1.7 to 3.7), and diabetes (OR = 2.1, 95% CI = 1.8 to 2.4) were all significantly higher in the patients with schizophrenia than in the comparison group. The differences were significant in both the crude and the adjusted analyses (Table 5). The point estimate of prevalence of ventricular arrhythmias was higher in the schizophrenia group than in the comparison group, although it was not statistically significant due to the small number of cases. The prevalence of AMI and non-AMI ischemic heart disease in the population with schizophrenia was not significantly different from that in the comparison population.

Incidence of ventricular arrhythmia, heart failure, stroke, and diabetes was significantly higher in the group with schizophrenia than in the comparison group (Table 6). The adjusted risk ratios between patients with schizophrenia and the comparison group were ventricular arrhythmia 2.3 (95% CI = 1.2 to 4.3), stroke 1.5 (95% CI = 1.2 to 2.0), diabetes 1.8 (95% CI = 1.2 to 2.6), and heart failure 1.6 (95% CI = 1.2 to 2.0). Incidence of AMI, non-AMI ischemic heart disease, arrhythmia, syncope, and TCI was not significantly different in the 2 groups.

All measures of mortality were significantly higher in the patients with schizophrenia than in the comparison

Table 4. Patients (N = 3022) With Schizophrenia Who Received Prescriptions for Antipsychotic Drugs, January 1994–March 1999[a]

Antipsychotic Agent	%
Any antipsychotic agent	86.9
Phenothiazines[b]	62.3
Chlorpromazine	21.6
Fluphenazine decanoate	17.5
Fluphenazine enanthate	0.3
Fluphenazine HCl	1.2
Mesoridazine	0.8
Pericyazine	0.9
Perphenazine	7.1
Pipotiazine	4.3
Prochlorperazine	2.5
Thioridazine	14.2
Trifluoperazine	23.0
Dibenzepine (loxapine)	5.5
Phenylbutylpiperadines[b]	34.2
Fluspirilene	0.5
Haloperidol	30.5
Pimozide	5.0
Novel agents[b]	32.3
Clozapine	4.9
Olanzapine	7.0
Quetiapine	0.4
Risperidone	27.8
Thioxanthenes[b]	23.0
Flupenthixol	20.4
Thiothixene	0.7
Zuclopenthixol	3.9

[a]Patients with prescriptions for more than 1 antipsychotic drug are counted for each drug.
[b]Patients with same-class prescriptions are counted only once in this summary figure.

group, even after adjustment for risk factors. The adjusted risk ratio of all-cause mortality was 2.8 (95% CI = 2.3 to 3.4). It is not only the suicide rate that was significantly higher in persons with schizophrenia: the rate of non-suicide death with cardiovascular contributing causes was significantly higher among patients with schizophrenia, with an adjusted risk ratio of 2.2 (95% CI = 1.7 to 2.8).

DISCUSSION

Ours is the first population-based study to evaluate the prevalence and incidence of cardiovascular outcomes in the population of patients with schizophrenia and compare these with outcomes of an internal comparison group. The study showed that the prevalence of cardiovascular morbidity, including arrhythmia, syncope, heart failure, stroke, TCI, and diabetes, was significantly higher among patients with schizophrenia than in the matched comparison population with no psychiatric diagnoses after adjusting for cardiovascular risk factors. Compared with that of a matched population, the incidence of ventricular arrhythmia, heart failure, stroke, diabetes, and cardiovascular mortality was significantly increased in patients with schizophrenia.

The prevalence of diabetes in the schizophrenia group (91.7/1000, Table 5) was comparable to the proportion of subjects reported to be under current treatment for diabetes in the Patient Outcomes Research Team (PORT) field study (93/1000).[2] The PORT study did not include a comparison group but found the prevalence of diabetes in patients with schizophrenia to be more than twice that of reported statistics for the general population. The results of our study showed a crude odds ratio of diabetes of 1.9 (95% CI = 1.6 to 2.2) for the schizophrenia group versus the matched comparison group and an adjusted odds ratio of 2.1 (95% CI = 1.8 to 2.4). Since the present study captured diagnosed diabetes and the PORT study captured treated diabetes, neither accounted for undiagnosed diabetes, and both are likely to have underestimated the true prevalence of diabetes. There is no evidence to suggest whether undiagnosed diabetes is more or less likely to occur in patients with schizophrenia or in the comparison group.

We found increased risk of all-cause mortality and cardiovascular mortality in individuals with schizophrenia as compared with an age- and sex-matched, randomly selected, general population comparison group. This finding is consistent with the excess all-cause mortality[5,6,8,12–15] and cardiovascular mortality[3,4,6,7] reported in previous studies. Brown's meta-analysis of 18 studies reports an overall mortality rate in schizophrenia of 1½ times expected mortality.[12] A recent study by Brown et al.[3] followed 370 patients in the United Kingdom over a 13-year period and found that death was 3 times more likely in the schizophrenia group than would have been expected given their age, sex, smoking, and "social disadvantage." The excess mortality is only in part due to a high rate of suicide.[12,16] Waddington and colleagues'[17] 10-year prospective study of mortality among schizophrenia patients in Ireland showed higher-than-expected mortality rates and no suicides.

A study of trends of schizophrenia mortality in Stockholm County, Sweden, by Osby et al.[6] showed that the standard mortality ratio for cardiovascular mortality increased substantially from the late 1970s to the mid-1990s. The standard mortality ratios for the periods 1976–1980, 1981–1985, 1986–1990, and 1991–1995 were 1.7, 2.0, 4.2, and 8.3 for males and 1.7, 2.1, 3.1, and 5.0 for females. In the Brown et al.[3] study, death caused by cardiovascular disease was almost twice as likely as expected. The authors suggest that this is, in part, due to the number of "avoidable deaths," including problems such as missed medical diagnoses and poor treatment compliance, that are related to the patients' confusion or psychoses. They also suggest that the excess mortality is due to unhealthy lifestyles, including smoking, poor diet, obesity, and lack of exercise.

Other researchers have found that obesity is higher in the population with schizophrenia and that it is associ-

Table 5. Prevalence of Cardiovascular Comorbidities Among Patients With Schizophrenia and Their Matched General Population Comparison Group in Saskatchewan, Canada, 1994–1995

Comorbidity	Prevalence (per 1000 patients): Patients With Schizophrenia (N = 3022)	Prevalence (per 1000 patients): Sample of General Population (matched) (N = 12,088)	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)[a]
Acute myocardial infarction	12.2	9.5	1.3 (0.9 to 1.9)	1.3 (0.9 to 1.9)
Ischemic heart disease	58.6	60.6	1.0 (0.8 to 1.1)	1.1 (0.9 to 1.3)
Arrhythmias	51.3	36.7	1.4 (1.2 to 1.7)	1.5 (1.2 to 1.8)
Ventricular arrhythmias	2.6	1.4	1.9 (0.8 to 4.4)	1.7 (0.7 to 3.9)
Syncope and collapse	5.3	1.6	3.4 (1.7 to 6.6)	4.0 (2.0 to 7.9)
Heart failure	46.3	29.8	1.6 (1.3 to 1.9)	1.7 (1.4 to 2.2)
Stroke	27.5	14.6	1.9 (1.5 to 2.5)	2.1 (1.6 to 2.7)
Transient cerebral ischemia	14.6	6.4	2.3 (1.6 to 3.4)	2.6 (1.7 to 3.7)
Diabetes	91.7	50.5	1.9 (1.6 to 2.2)	2.1 (1.8 to 2.4)

[a]Odds ratios are adjusted for age, sex, and medical risk factors using logistic regression. The risk factors used varied by outcome, as follows: arrhythmia and acute myocardial infarction were adjusted for hypertension and diabetes; ventricular arrhythmia was adjusted for diabetes; syncope was adjusted for hypertension and prior cardiovascular disease; stroke was adjusted for hypertension, hyperlipidemia, diabetes, and combination of hypertension and hyperlipidemia; transient cerebral ischemia was adjusted for hypertension, hyperlipidemia, diabetes, and serious pulmonary disease; heart failure and ischemic heart disease were adjusted for hypertension, diabetes, hyperlipidemia, serious pulmonary disease and the combinations hypertension/hyperlipidemia, diabetes/hyperlipidemia, hypertension/diabetes.

Table 6. Incidence of Cardiovascular Comorbidities Among Patients With Schizophrenia and Their Matched General Population Comparison Group in Saskatchewan, Canada, January 1996–March 1999

Comorbidity	Incidence (per 1000 person-years): Patients With Schizophrenia (N = 2405)	Incidence (per 1000 person-years): Sample of General Population (matched) (N = 9175)	Unadjusted Risk Ratio (95% CI)	Adjusted Risk Ratio (95% CI)[a]
Acute myocardial infarction	4.3	5.0	0.9 (0.6 to 1.2)	0.9 (0.6 to 1.4)
Ischemic heart disease	17.4	15.8	1.1 (0.9 to 1.3)	1.1 (0.9 to 1.4)
Arrhythmias	16.5	14.2	1.2 (1.0 to 1.4)	1.2 (1.0 to 1.5)
Ventricular arrhythmias	1.7	0.8	2.0 (1.1 to 3.8)	2.3 (1.2 to 4.3)
Syncope and collapse	1.7	1.1	1.5 (0.8 to 2.7)	1.7 (0.9 to 3.4)
Heart failure	13.3	9.8	1.4 (1.1 to 1.7)	1.6 (1.2 to 2.0)
Stroke	7.5	5.6	1.3 (1.0 to 1.8)	1.5 (1.2 to 2.0)
Transient cerebral ischemia	3.5	4.1	0.9 (0.6 to 1.3)	1.0 (0.6 to 1.5)
Diabetes	7.0	4.3	1.6 (1.2 to 2.2)	1.8 (1.2 to 2.6)
All-cause mortality	30.4	11.3	2.7 (2.3 to 3.1)	2.8 (2.3 to 3.4)
Suicide[b]	1.1	0.2	6.8 (2.5 to 18.7)	…
Sudden death[c]	1	0.3	3.4 (1.4 to 8.1)	…
Cardiovascular disease mortality	10.8	5.3	2.0 (1.6 to 2.5)	2.2 (1.7 to 2.8)

[a]Risk ratios were adjusted for age, sex, and medical risk factors using Poisson regression. The risk factors used varied by outcome as follows: arrhythmia, ventricular arrhythmia, transient cerebral ischemia, all-cause mortality, and cardiovascular mortality models adjusted for hypertension, hyperlipidemia, diabetes, serious pulmonary disease, cardiovascular disease and presence of more than 1 of these diseases; acute myocardial infarction and stroke models adjusted for the previously listed medical risk factors except serious pulmonary disease; syncope model adjusted for hypertension, any factor other than hypertension, and the presence of more than 1 disease; diabetes model adjusted for hypertension, hyperlipidemia, cardiovascular disease, and the presence of more than 1 disease; heart failure and ischemic heart disease models adjusted for hypertension, diabetes, hyperlipidemia, serious pulmonary disease, and the presence of more than 1 disease.
[b]No multivariate adjusted model was constructed for suicide.
[c]There were not enough cases for a risk-adjusted model of sudden death to converge.
Symbol: … = no risk-adjusted model.

ated with higher mortality rates, coronary heart disease, strokes, and diabetes.[18] Other studies have found associations between antipsychotic drugs and cardiovascular outcomes.[19–21] In the present study, we did not analyze the relationship of exposure to antipsychotic medications with each outcome.

This study has several strengths. First, Saskatchewan Health services data represent a population with universal health care coverage and consequently capture an entire geographic area without enrollment bias due to economic status, employment status, health care payment method, or age. Second, patients included in this study were representative of the overall schizophrenia patient population in Saskatchewan since both inpatient and outpatient diagnosed schizophrenia patients were included. Third, the occurrence and date of death were verified against the vital statistics data, which include all deaths registered in Saskatchewan. And fourth, we were able to adjust the comparison of schizophrenia patients with the internal comparison group for several cardiovascular risk factors.

The major limitations of this study are as follows. (1) Schizophrenia patients and cardiovascular outcomes were identified by the ICD-9 codes or a combination of ICD-9 codes and medication dispensing in claims data. Due

to limited resources, we were unable to review medical records to validate the diagnoses. However, a wide range of conditions has been validated in Saskatchewan Health services databases, including schizophrenia and ischemic heart disease.[10,11] (2) The adjustments for cardiovascular risk factors were limited to the information collected in administrative data. We were unable to adjust for some important cardiovascular risk factors in the analysis, such as smoking, body weight, and alcohol and substance abuse. (3) Patients treated exclusively by a salaried psychiatrist were unlikely to be identified for the study unless they were hospitalized.

In summary, the findings of this population-based study indicate that patients with schizophrenia have an increased burden of cardiovascular comorbidities and mortality. Whether this is related to the natural history of schizophrenia, unhealthy lifestyles, "social disadvantage" of schizophrenia patients, or treatments for schizophrenia remains to be elucidated in future studies.

Drug names: bumetanide (Bumex and others), chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril and others), digoxin (Lanoxin, Lanoxicaps, and others), ethacrynic acid (Edecrin), fluphenazine (Prolixin, Permitil, and others), furosemide (Lasix and others), haloperidol (Haldol and others), loxapine (Loxitane and others), mesoridazine (Serentil), olanzapine (Zyprexa), perphenazine (Trilafon and others), pimozide (Orap), prochlorperazine (Compazine, Compro, and others), quetiapine (Seroquel), risperidone (Risperdal), thiothixene (Navane and others), trifluoperazine (Stelazine and others).

REFERENCES

1. Dixon L, Postrado L, Delahanty J, et al. The association of medical comorbidity in schizophrenia with poor physical and mental health. J Nerv Ment Dis 1999;187:496–502
2. Dixon L, Weiden P, Delahanty J, et al. Prevalence and correlates of diabetes in national schizophrenia samples. Schizophr Bull 2000;26: 903–912
3. Brown S, Inskip H, Barraclough B. Causes of the excess mortality of schizophrenia. Br J Psychiatry 2000;177:212–217
4. Allebeck P. Schizophrenia: a life-shortening disease. Schizophr Bull 1989;15:81–89
5. Newman SC, Bland RC. Mortality in a cohort of patients with schizophrenia: a record linkage study. Can J Psychiatry 1991;36:239–245
6. Osby U, Correia N, Brandt L, et al. Time trends in schizophrenia mortality in Stockholm County, Sweden: cohort study. BMJ 2000;321:483–484
7. Mortensen PB, Juel K. Mortality and causes of death in schizophrenic patients in Denmark. Acta Psychiatr Scand 1990;81:372–377
8. Black DW, Fisher R. Mortality in DSM-III-R schizophrenia. Schizophr Res 1992;7:109–116
9. Downey W, Beck P, McNutt M, et al. Health databases in Saskatchewan. In: Strom BL, ed. Pharmacoepidemiology. 3rd ed. Chichester, England: John Wiley & Sons; 2000:325–345
10. Rawson NS, Malcolm E, D'Arcy C. Reliability of the recording of schizophrenia and depressive disorder in the Saskatchewan health care data files. Soc Psychiatry Psychiatr Epidemiol 1997;32:191–199
11. Rawson NSB, Malcolm E. Validity of the recording of ischemic heart disease and chronic obstructive pulmonary disease in the Saskatchewan health care datafiles. Stat Med 1995;14:2627–2643
12. Brown S. Excess mortality of schizophrenia. Br J Psychiatry 1997;171:502–508
13. Hannerz H, Borga P, Borritz M. Life expectancies for individuals with psychiatric diagnoses. Public Health 2001;115:328–337
14. Bralet MC, Yon V, Loas G, et al. Mortality in schizophrenia: an 8-year follow-up study in 150 chronic schizophrenics [in French]. Encephale 2000;26:32–41
15. Joukamaa M, Heliovaara M, Knekt P, et al. Mental disorders and cause-specific mortality. Br J Psychiatry 2001;179:498–502
16. Goldman LS. Medical illness in patients with schizophrenia. J Clin Psychiatry 1999;60(suppl 21):10–15
17. Waddington JL, Youssef HA, Kinsella A. Mortality in schizophrenia: antipsychotic polypharmacy and absence of adjunctive anticholinergics over the course of a 10-year prospective study. Br J Psychiatry 1998;173:325–329
18. Aronne LJ. Epidemiology, morbidity, and treatment of overweight and obesity. J Clin Psychiatry 2001;62(suppl 23):13–22
19. Haupt DW, Newcomer JW. Hyperglycemia and antipsychotic medications. J Clin Psychiatry 2001;62(suppl 27):15–26
20. Kilian JG, Kerr K, Lawrence C, et al. Myocarditis and cardiomyopathy associated with clozapine. Lancet 1999;354:1841–1845
21. Glassman AH, Bigger JT. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. Am J Psychiatry 2001;158: 1774–1782