Cardiovascular Disease Mortality in Patients With Chronic Schizophrenia Treated With Clozapine: A Retrospective Cohort Study

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Background: Cardiovascular disease (CVD) mortality in schizophrenia is more frequent than in the general population. Whether second-generation antipsychotics (SGAs) increase risk of CVD morbidity and mortality has yet to be determined.

Method: We conducted a retrospective cohort study using an administrative database to identify patients with *DSM-III–* or *DSM-IV*–diagnosed schizophrenia, treated in Maryland, who started clozapine treatment (n = 1,084) or were never treated with clozapine (initiated on risperidone; n = 602) between 1994 and 2000. Deaths between 1994 and 2004 were identified by the Social Security Death Index, and death records were obtained.

Results: During the 6- to 10-year follow-up period, there were 136 deaths, of which 43 were attributed to CVD. Cardiovascular disease mortality in patients aged younger than 55 years at medication start was approximately 1.1% (clozapine, 1.1%; risperidone, 1.0%) in both groups at 5 years and 2.7% (clozapine) and 2.8% (risperidone) at 10 years ($\chi^2_1 = 0.12$, $P = .73$). Patients who started treatment at ages ≥ 55 years had CVD mortality of 8.5% (clozapine) and 3.6% (risperidone) at 5 years and 16.0% (clozapine) and 5.7% (risperidone) at 10 years ($\chi^2_1 = 2.13$, $P = .144$). In a Cox regression model, patients aged ≥ 55 years were at greater risk of mortality than younger patients (hazard ratio = 4.6, $P < .001$); whites were at greater risk than nonwhites (HR = 2.1, $P = .046$); however, SGA treatment (HR = 1.2; 95% CI, 0.6–2.4; $P = .61$) and sex (HR = 0.9, $P = .69$) were not statistically significant predictors of CVD, nor was there a significant age × clozapine interaction ($\chi^2_1 = 1.52$, $P = .22$). Age-, race-, and gender-adjusted standardized mortality ratios were significantly elevated (clozapine, 4.70; 95% CI, 3.19–6.67; risperidone, 2.88; 95% CI, 1.38–5.30) compared to year 2000 rates for the Maryland general population but did not differ by antipsychotic group ($\chi^2_1 = 1.42$, $P = .23$).

Conclusions: The risk of CVD mortality in schizophrenia does not differ between clozapine and risperidone in adults despite known differences in risk profiles for weight gain and metabolic side effects. However, we cannot rule out an increased risk of CVD mortality among those starting treatment at ages 55 years or older.

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Individuals with schizophrenia are known to have excessive morbidity and mortality compared to the general population.[1] This increased mortality rate is estimated to be up to 5 times higher[2–5]—the life expectancy is estimated to be about 15 years less than those without severe mental illness[6]—and all-cause mortality rates have increased during recent decades.[5] A meta-analysis of mortality rates reported that people with schizophrenia have higher rates of death from natural and unnatural causes than those with other mental disorders.[4] Deaths from cardiovascular-related events are believed to occur more frequently in people with schizophrenia than in the healthy population. A study of coroner files by Ruschena and colleagues[7] reported the relative risk of people with schizophrenia having cardiovascular disease (CVD) as 4.9 times higher than the general population. More than two-thirds of these people, compared with approximately one-half in the general population, reportedly die of CVD.[6]

The prevalence of risk factors for CVD is 1.5–2.0 times higher in people with schizophrenia than in the general population.[8] Poor lifestyle habits most likely contribute to increases in morbidity and mortality in people with schizophrenia. These habits include lack of exercise and sedentary life style, poor diet, obesity, cigarette smoking, and other types of substance abuse.[9] Compared to the general population, people with schizophrenia consume fewer fruits, vegetables, and dairy products and are less physically active.[10] Other contributors to the increase include psychosocial factors such as depression, social isolation and low socioeconomic status, less access to medical care, lower overall use of medical care, and lower compliance with treatment regimens.[6] In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trials,[11] rates of nontreatment in people with schizophrenia for diabetes, hypertension, and dyslipidemia were 30%, 62%, and 88%, respectively.[12] Co-occurring metabolic disturbances, such

as insulin resistance, diabetes, and dyslipidemia, may also contribute to increased risks for CVD morbidity and mortality in the schizophrenia population,[6] and the prevalence of metabolic disturbances is on the rise.[13] Approximately 50% of individuals with schizophrenia have a serious co-occurring physical illness.[1] Results from the CATIE trials[11] and the Cardiovascular, Lipid, and Metabolic Outcomes Research in Schizophrenia (CLAMORS) study[12] estimate that 10-year CVD risk is significantly elevated in patients with schizophrenia compared to controls.[14] The CATIE trial also found that the prevalence of cigarette smoking was higher than in controls (68% vs 35%), as was diabetes (13% vs 3%) and hypertension (27% vs 17%). The risk for metabolic syndrome in people with psychosis is significantly greater than in the general population.[15] The prevalence of metabolic syndrome among people with schizophrenia generally ranges from 19%–35% in European samples[12,15–22] and from 35%–52% in US samples.[16,23]

Antipsychotic treatment has also been scrutinized as potentially adding to the risk of CVD-related morbidity and mortality in people with schizophrenia.[24,25] Clozapine is the only antipsychotic medication approved for treatment-resistant schizophrenia, and the superiority of this second-line antipsychotic compared to risperidone is well established.[26] Clozapine, however, causes significant increases in risk factors for cardiovascular disease. In addition to the low risk for myocarditis and cardiomyopathy,[27,28] clozapine causes significant weight gain and may contribute to the risk of developing diabetes mellitus and other metabolic abnormalities.[29–32] However, there have been no studies directly testing whether clozapine increases CVD mortality risk compared to other antipsychotics. It has been estimated that weight gain associated with second-generation antipsychotics (SGAs) may lead to an increase in mortality to over 400 additional deaths per 100,000 patients with schizophrenia per decade.[33] In a recent review of mortality in schizophrenia, Auquier et al[34] reported that while, indeed, unhealthy lifestyles, polypharmacy, and inadequate health care have been shown to contribute to the high natural mortality, the link between the use of antipsychotics and mortality has not been clarified. Osborn et al[35] also recently completed a large study examining the relative risk of cardiovascular mortality in people with severe mental illness using the United Kingdom's general practice research database from a community sample. This study reported that the risk of death from CVD is not wholly explained by antipsychotic medication use. Likewise, Enger et al[36] found that mortality was 4 times higher in people with schizophrenia compared to the control group regardless of whether patients were treated with typical or atypical antipsychotic medications. Filik et al[37] also reported that much of the increased risk for cardiovascular morbidity may be explained by lifestyle risk factors. Others, however, have reported that a significant increase in the prevalence of obesity and diabetes mellitus had been observed in the late 1990s, which may be related to second-generation antipsychotic use.[38] These data suggest that future CVD mortality will most likely be increased by these factors.

This study aimed to determine if clozapine use was associated with an elevated risk of CVD mortality in patients with chronic schizophrenia as compared to chronic patients with chronic schizophrenia never exposed to clozapine treatment.

METHOD

Study Population

The retrospective cohort study population consisted of persons with a *Diagnostic and Statistical Manual of Mental Disorders*, Third or Fourth Edition (*DSM-III* or *DSM-IV*) diagnosis of schizophrenia, schizoaffective disorder, or psychosis not otherwise specified from the state of Maryland between January 1, 1994, and May 31, 2000 and were between 20 and 69 years of age at the time of the first prescription with either clozapine or risperidone. The clozapine sample was identified from a large preexisting database of persons treated with this agent through medical or pharmacy assistance in the state of Maryland maintained by the Clozapine Authorization and Monitoring Program in Maryland. The control group was persons initiated on risperidone during inpatient treatment in Maryland who had never received clozapine treatment at any point in their lives, identified from an administrative database recording inpatient use of SGAs in Maryland. Those initiated on risperidone were selected to provide a control group treated with an antipsychotic whose associated profile of weight and metabolic changes should lead to lower increase in cardiac risk than clozapine treatment. This control group included patients ill enough to be hospitalized, who could have been treated with various other antipsychotics (quetiapine, conventional antipsychotics) but never clozapine; thus, it represents, generally, a sample of severely ill patients on antipsychotics and never treated with clozapine. Patients in the risperidone group subsequently initiated on clozapine or treated with olanzapine (which resembles clozapine in its metabolic effects) in the inpatient setting were also excluded, thus lowering the number of control subjects. We will refer to this group as the risperidone, or control antipsychotic, group; however, it more broadly reflects nonclozapine treatment. The beginning time period of 1994 was selected to minimize any difference in secular trends in mortality, since risperidone was first introduced into the marketplace in 1994. This protocol was approved by the University of Maryland and state of Maryland institutional review boards. A waiver was granted for informed consent due to the low-risk nature of the study and the fact that many persons included were deceased.

Identifying Deceased Persons

To identify deceased subjects, patient records selected from the above sources were matched with the Social

Security Death Index (SSDI) database, which records reported death dates and locations for all US citizens who paid social security taxes or received social security benefits. Records from the SSDI from 1994 through December 31, 2004 were extracted on 2 separate occasions—in early 2002 and in late 2005—to allow sufficient time lag for deaths to be entered into the SSDI. Follow-up for mortality lasted 6–10 years, depending on when patients started clozapine or risperidone. Patients were identified in the SSDI by their social security numbers. Two research assistants independently entered all social security numbers into the death index (H.W., T.W.). If this number was incorrect or absent, patients were matched between SSDI and Maryland databases if their full names and dates of birth were identical in both databases. Death certificates were collected from the Maryland Division of Vital Records. Death certificates were available for all subjects in this study who died.

Data Analysis

Cardiovascular disease–related deaths were identified from death certificates. Cardiovascular disease deaths included atherosclerotic CVD, hypertensive CVD, coronary artery disease, coronary vessel disease, coronary occlusion, congestive heart failure secondary to CVD, myocardial infarction with underlying CVD, myocarditis, dilated cardiomyopathy, and cardiac arrhythmia with underlying CVD. Cardiovascular disease death did not include myocardial infarction secondary to other causes (cancer, asphyxia, infection) and cerebral vascular disorders (cerebral vascular attack, stroke, or cerebral hemorrhage).

The distribution of time to cardiac-related death for each treatment was estimated using the Kaplan-Meier[39] method of survival analysis, with follow-up censored at December 31, 2004. The primary study analysis compared the distribution of time to death in clozapine- and risperidone-treated patients using the log-rank test,[40] stratified by age at start of treatment (<55 and ≥ 55). Analyses were stratified by age to take account of differences between treatments in the age at which patients started the treatment of interest, with a higher percentage of risperidone-treated patients in the high CVD risk age group of ≥ 55 years old.

The Cox proportional hazards life regression model[41] was used to estimate hazard ratios (HRs) for risk factors associated with CVD mortality (age, race, sex, and antipsychotic treatment). Treatment × race, treatment × sex, and treatment × age interactions were explored but dropped from the final model if not nominally significant ($P<.05$). Racial distinction was missing on 235 subjects. Treatments were compared on demographic variables using χ^2 tests or student *t* tests where appropriate. All tests were 2-sided comparisons with an $\alpha=.05$.

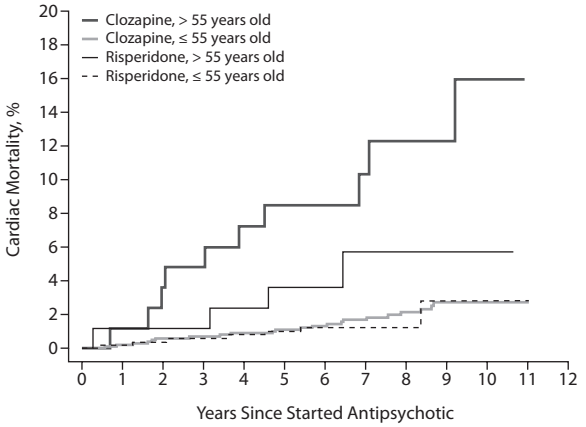
Age-, gender-, and race-adjusted standardized mortality ratios (SMRs) were calculated comparing CVD death rates among persons with schizophrenia with the Maryland general population ages 20–69, using US Census estimates of the year 2000 total population by race (white vs nonwhite), gender, and 5-year age group (20–24, 25–29, …, 65–69); counts for CVD deaths in the Maryland general population in the year 2000 were obtained from the Vital Statistics Administration at the Department of Health and Mental Hygiene in Baltimore, Maryland, using *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes matching CVD deaths contained in the antipsychotic sample (i00–i09 + i11 + i13 + i20–i51). Within each age, sex, and race stratum of the study sample, "expected" schizophrenic deaths were calculated by the formula $E_k = y_{sk}d_{pk} \div n_{pk}$, where y_{sk} is the number of person-years of exposure in the k-th stratum among people with schizophrenia, d_{pk} is the number of cardiac deaths within the k-th stratum in the Maryland population in the year 2000, and n_{pk} is the estimated Maryland population within the k-th stratum in the year 2000. Patients contributed person-years of exposure within a particular age-stratum as long as their age fell within that stratum, after which they contributed exposure to the next stratum until they died or were censored by the end of mortality follow-up in 2004. The SMR is calculated by $SMR = (\Sigma_k O_k) / (\Sigma_k E_k)$—the total number across all k strata of observed deaths, O_k, among persons with schizophrenia, divided by the total number of expected deaths across all k strata.[42] Confidence intervals for SMRs were calculated using Byar's approximation.[43] Similar methods were used to calculate SMRs for gender- and race-specific subgroups within the schizophrenia sample. Tests for differences between SMRs for clozapine versus risperidone, males versus females, and whites versus nonwhites were calculated as follows: let O_1 and O_2 be observed deaths in groups 1 and 2 and E_1 and E_2 the expected deaths in groups 1 and 2 based on the standard population; $O = O_1 + O_2$ equals the total deaths observed and $E = E_1 + E_2$ equals the total number of deaths expected. Then, with $E^*_1 = O(E_1 / E)$ and $E^*_2 = O(E_2 / E)$, the equation $\chi^2 = [(O_1 - E^*_1) - 1/2]^2 / E^*_1 + [(O_2 - E^*_2) - 1/2]^2 / E^*_2$ gives a χ^2 test with 1 degree of freedom for differences in the SMR between groups 1 and 2.[42]

RESULTS

Demographic Information

A total of 1,686 subjects, 964 with schizophrenia (57%), 561 with schizoaffective disorder (33%), and 161 with psychotic disorder not otherwise specified (10%) were included in the study; 1,084 subjects were treated with clozapine, and 602 subjects were in the risperidone group. Sixty-four percent of the clozapine group ($n=690$) was male, as was 61% of the risperidone group ($n=369$) ($\chi^2_1 = 0.84$, $P=.36$). The mean age at start of treatment was 39.0 ± 9.8 years (range, 20.1–69.5) in the clozapine group and 41.2 ± 11.7 years (range 20.2–70.0) in the risperidone group ($t_{1073} = 4.03$, $P<.0001$). In the clozapine group, 85 of 1,084 (7.8%) patients were older than 55 years, compared to 86 of 602 (14.3%) patients older than 55 years in the risperidone

Figure 1. Kaplan-Meier Estimates of Cumulative Probability of Cardiovascular Death by Years of Follow-Up, Age, and Antipsychotic Treatment[a]



[a]Tests of mortality differences from the Cox proportional hazards model: age, $P < .0001$; treatment, $P = .61$; age × treatment, $P = .22$.

Table 1. Life Regression Analysis for Risk of Cardiovascular Disease Mortality[a]

Variable	Hazard Ratio (95% CI)	χ^2	*P* Value
Race (white)	2.06 (1.01–4.21)	3.98	.046
Antipsychotic treatment	1.20 (0.59–2.44)	0.26	.613
Sex (male)	0.88 (0.47–1.64)	0.16	.688
Age 55–69 y	4.55 (2.31–8.98)	19.17	< .0001

[a]Treatment × age: $\chi^2_1 = 1.52$, $P = .22$.
Treatment × race: $\chi^2_1 = 0.06$, $P = .81$.
Treatment × sex: $\chi^2_1 = 0.40$, $P = .53$.

group ($\chi^2_1 = 17.64$, $P < .0001$). In the clozapine group, 62.9% were white, 33.2% African American, and 3.9% other, and in the risperidone group, 47.8% were white, 49.7% African American, and 2.5% other ($\chi^2_2 = 37.84$, $P < .0001$).

In a subsample of this study, clinical data were available; however, for the majority of subjects, clinical data were not available. The mean Global Assessment of Functioning (GAF) scores were 37.8 ± 10.7 and 37.5 ± 11.0 in the clozapine (n = 326) and risperidone (n = 396) groups, respectively ($t_{720} = 0.29$, $P = .77$). The mean weights were 80.1 ± 17.3 kg and 78.2 ± 18.4 kg in the clozapine (n = 251) and risperidone (n = 295) groups, respectively ($t_{544} = 1.25$, $P = .21$). Similar percentages in each group had substance abuse histories (clozapine, 75.8%, n = 260; risperidone, 72.8%, n = 345; $\chi^2_1 = 0.70$, $P = .40$); however, a significantly greater percentage of patients were smokers in the clozapine group (61.0%, n = 372) compared to the risperidone group (47.7%, n = 442; $\chi^2_1 = 14.3$, $P = .0002$).

Cardiac-Related Mortality

Cardiac causes accounted for 34.8% (32/92) and 25.0% (11/44) of the clozapine and risperidone group deaths, respectively. As expected, after stratifying on age (≤ 55, > 55) at antipsychotic start, mortality for both antipsychotic groups was considerably higher in the older group (Figure 1). People who were younger than 55 years when started on clozapine and risperidone had respective estimate CVD mortality risks of 1.1% and 1.0% at 5 years and 2.7% and 2.8% at 10 years ($\chi^2_1 = 0.12$, $P = .73$ for drug effect). Patients with schizophrenia initiated on clozapine and risperidone aged ≥ 55 years had respective CVD mortality risks of 8.5% and 3.6% at 5 years and 16.0% and 5.7% at 10 years ($\chi^2_1 = 2.13$, $P = .144$ for drug effect) (see Figure 1). After further adjustment for age (≤ 55, > 55), race, and sex, a Cox regression analysis (Table 1) found no evidence for treatment × age interaction ($\chi^2_1 = 1.52$, $P = .22$); after deleting nonsignificant interactions, the Cox model found no significant difference in cardiac mortality rates between patients treated with clozapine versus risperidone (HR = 1.20, $\chi^2_1 = 0.255$, $P = .613$). Compared to patients with ages ≤ 55, patients with ages > 55 had significantly increased cardiac mortality (HR = 4.6, $\chi^2_1 = 19.2$, $P < .0001$). Sex (HR = 0.9, $P = .69$) was not a significant predictor of mortality; however, white race was a significant predictor of mortality (HR = 2.1, $\chi^2_1 = 3.98$, $P = .046$).

Standardized Mortality Ratios

Age-, race-, and sex-adjusted CVD SMRs comparing patients with schizophrenia to the Maryland general population in the year 2000 (Table 2) show significantly elevated mortality for both clozapine (SMR = 4.7; 95% CI, 3.2–6.7) and risperidone (SMR = 2.9; 95% CI, 1.4–5.3); consistent with the Cox model, the difference in SMRs for the 2 antipsychotic groups was not significant ($\chi^2 = 1.42$, $P = .23$). The CVD SMR for whites with schizophrenia (SMR = 6.5) was notably higher than for nonwhites (1.9; $\chi^2_1 = 11.63$, $P = .001$). The SMRs for males and females were significantly different (3.2 vs 6.3, $\chi^2_1 = 3.96$, $P = .047$). As noted above, information on ethnicity was not available for about one-quarter (n = 131) of patients on risperidone, but this information was not available in a much smaller fraction of patients (n = 6) on clozapine, who could not be included in calculating SMRs shown in Table 2. Accordingly, we calculated CVD mortality ratios standardized by age and sex alone (Table 3), which gave similar results, although point estimates of the relative excess in mortality among patients with schizophrenia treated with clozapine compared to patients treated with risperidone or to the general population were slightly higher than when race was incorporated as an adjustment factor.

DISCUSSION

To our knowledge, this is the first study to examine mortality in a sample of people with chronic schizophrenia treated with clozapine compared to an antipsychotic group with a lower weight gain potential. In our study, we did not find any difference in the risk of CVD mortality

Table 2. Cardiovascular Disease Mortality in Maryland Persons With Schizophrenia: Age-, Race-, and Sex-Adjusted Standardized Mortality Ratios (SMRs) Compared to the Maryland General Population in 2000[a]

	Overall (n = 1,549)		Clozapine (n = 1,078)		Risperidone (n = 471)		Test for Clozapine-Risperidone Difference	
	SMR	95% CI	SMR	95% CI	SMR	95% CI	χ^2_1	*P* Value
Male	3.20	2.03–4.81	3.82	2.26–6.03	2.03	0.65–4.74	1.11	.293
Female	6.25	3.70–9.88	6.92	3.68–11.84	4.98	1.61–11.63	0.14	.704
White	6.45	4.38–9.15	7.06	4.52–10.50	4.98	2.00–10.26	0.38	.537
Nonwhite	1.90	0.91–3.50	2.19	0.88–4.52	1.46	0.29–4.25	0.08	.783
All patients	4.08	2.92–5.53	4.70	3.19–6.67	2.88	1.38–5.30	1.42	.233

[a]Test for male-female difference in SMR (pooling across drug): $\chi^2_1 = 3.96$, $P = .047$; test for white-nonwhite difference (pooling across drug): $\chi^2_1 = 11.63$, $P = .001$.

Table 3. Cardiovascular Disease Mortality in Maryland Persons With Schizophrenia: Age- and Sex-Adjusted Standardized Mortality Ratios (SMRs) Compared to the Maryland General Population in 2000[a]

	Overall (N = 1,686)		Clozapine (N = 1,084)		Risperidone (N = 602)		Test for Difference	
	SMR	95% CI	SMR	95% CI	SMR	95% CI	χ^2_1	*P* Value
Male	3.18	2.01–4.77	3.91	2.31–6.17	1.90	0.61–4.44	1.53	.216
Female	6.05	3.58–9.56	7.00	3.72–11.97	4.48	1.44–10.45	0.38	.540
All patients	4.02	2.88–5.45	5.01	3.40–7.11	2.80	1.34–5.14	2.13	.144

[a]Test for male-female difference in SMR (pooling across drug): $\chi^2_1 = 3.649$, $P = .056$.

with clozapine as compared to nonclozapine treatment with risperidone in those aged less than 55 years. Five- and 10-year risk estimates for CVD mortality were very similar between groups after stratification on age, with no indication of mortality risk differences in people who start antipsychotics before the age of 55 years. In the group who started these antipsychotics at an older age (> 55), there was a trend toward higher cardiovascular mortality with clozapine (10-year CVD mortality estimate of 16.0% vs 5.7%, $P = .14$). The clozapine group included fewer African Americans, a group with lower CVD mortality in the patients sampled. Apparent differences in CVD mortality between clozapine and risperidone patients appeared restricted to patients started on these treatments after age 55 years but were not statistically significant; adjustment for age, sex, and race in a Cox model found no significant evidence ($P = 0.22$) for an age × treatment interaction, which would have confirmed the suggestion in the unadjusted data that there was an increased CVD risk associated with clozapine in older patients. Given the relatively limited number of older patients in our sample, we cannot rule out that in older people, clozapine may have a more detrimental effect on cardiovascular mortality than risperidone. The issue of clozapine in the elderly is likely complex. This population aged ≥ 55 years has many concomitant diseases and medications, and the use of clozapine in this population requires careful consideration.[44] Clozapine has been associated with higher heart rate and lower heart rate variability as compared to other antipsychotics and normal controls,[45] which may converge with the fact that elderly also have a lower vagal tone,[46] and low heart rate variability is a risk factor for cardiac death in the general population.[47,48] Moreover, it is possible that patients who start clozapine at younger ages might, with longer follow-up than the current, prove to be at increased risk of CVD mortality due to the cumulative effects of long-term exposure to the adverse metabolic effects of clozapine. It is encouraging that in the current study, despite the weight gain and adverse metabolic profile associated with clozapine, a notable increase in CVD mortality was not seen among clozapine-treated patients with schizophrenia aged < 55 years old compared to the risperidone group.

While the metabolic risks associated with clozapine should not be discounted, it should be noted that the causes of increased cardiovascular mortality in persons with schizophrenia are likely complex and not solely due to antipsychotic side effects on prevalence of the metabolic syndrome. Relative to the general population, mortality may be increased due to physiologic risks inherent to schizophrenia, poor lifestyles, and high rates of preexisting obesity and cardiovascular risk factors as opposed to being driven by antipsychotic effects. A previous study by our group examining autopsy records found that in people with schizophrenia, weight and visceral fat at the time of death were not higher in those with CVD than in the non-CVD deaths, unlike the association noted in autopsies of normal controls.[49] Furthermore, we have analyzed autopsy findings from people treated with clozapine and risperidone and found that there are no differences in cardiac findings in younger patients (mean age 44 years) who have died.[50] This is further evidence that factors other than weight and metabolic side effects must play a significant role in excess CVD mortality in persons with schizophrenia.

In the general population, men are typically at a higher risk than premenopausal women for CVD mortality,[51] and nonwhites at higher risk than whites.[52] It is notable that our study found no significant difference in CVD risk in males versus females among people with schizophrenia, although

we could not take account of menopausal status. Similarly, both Osborn et al[35] and Saha and colleagues[5] found the risk of cardiovascular mortality to be similar in both sexes in people with schizophrenia, with both studies suggesting a greater risk for females than the general population. More recent reports, however, demonstrated that females with schizophrenia are at equal or higher risk as males of the metabolic syndrome, meeting criteria for waist circumference criterion of metabolic syndrome and diabetes,[12,17,23] which may explain the findings of our study. Consistent with similar CVD risk for both genders among people with schizophrenia (unlike the general population), the excess CVD risk relative to the general population was considerably higher for females than males in our study (SMRs of 6.2 vs 3.2, respectively, $P = .047$). Again, in notable contrast to the general population, in our study, there was a suggestion that whites were at higher CVD mortality risk than nonwhites in both the Cox model (HR = 2.06, $P = .046$) and the SMR calculations (SMRs of 6.4 vs 1.9, $P = .001$). These data relating to racial differences need to be interpreted with caution, as race was not available in 131 subjects in the control group.

Independent of antipsychotic treatment, persons with schizophrenia had a significantly elevated risk of CVD mortality (clozapine SMR = 4.7, risperidone SMR = 2.9). Several others have examined mortality in schizophrenia and have consistently found a higher risk of CVD mortality in persons with schizophrenia as compared to controls (see Hennekens et al[6]). A few studies have suggested that antipsychotics may contribute to the excess mortality in schizophrenia,[53–56] and 1 study reported that antipsychotic polypharmacy contributed to mortality in schizophrenia[56]; however, no large-scale direct study of antipsychotic effects on mortality have been published, and the role of antipsychotics in the excess mortality, particularly cardiac-related mortality, remains unclear.[34] A very recent study[35] using the United Kingdom's General Practice Research Database reported that the risk of CVD mortality was not different between conventional and atypical antipsychotics in a sample of over 46,000 people with severe mental illness. Interestingly, this study also reported that the risk of CVD mortality was elevated, relative to controls, even in patients not receiving antipsychotic medications. However, this study included only people registered to general practitioners and would most likely not include people with chronic and treatment-refractory schizophrenia. Additionally, this study, along with others, did not specifically compare clozapine to other atypical antipsychotics, despite clozapine's potentially more severe cardiovascular risk due to its possible links to rare cardiac complications (myocarditis, cardiomyopathy) and substantial increases in weight and metabolic side effects. Lastly, the majority of studies examining mortality risk with antipsychotic treatment in schizophrenia have occurred in Europe, which may reflect different environmental risk factors for mortality, different patterns of antipsychotic use, and larger and more comprehensive databases and registries for linking prescription data.

We selected mortality rather than cardiovascular morbidity as the most robust outcome of cardiac-related sequelae of treatment and an easier endpoint for data ascertainment. Mortality reflects both incidence of a disease and its outcome[57]; however, we recognize that noncardiovascular morbidities associated with antipsychotics, such as hyperglycemia and dyslipidemia, while they may not be primary causes of death, are in themselves of serious concern. We are also limited by the fact that death as an indicator of disease prevalence can be complicated by possible inaccuracy in the recorded cause of death. Other limitations to the study include the lack of data on concomitant medications, previous treatments, routine clinical care and frequency of visits, smoking, substance abuse, concomitant disorders, plasma blood levels, lifestyle choices, and diets, which undoubtedly play a significant role in the risk of developing CVD. Nevertheless, we have no reason to suspect that these differed substantially among clozapine and other antipsychotic-treated patients. Patients initiated on risperidone in the inpatient mental health system were used as a comparison group, since this first-line antipsychotic has been in the marketplace for the longest time period and has a somewhat more benign profile than clozapine, with respect to weight gain and metabolic effects.[58] The subjects taking risperidone might have been treated with other antipsychotics, but they never received inpatient treatment with clozapine. It is possible that subjects with a high preexisting risk for CVD were less likely to be prescribed clozapine; however, the patient cohort selected received initial prescriptions of clozapine or risperidone from 1994 to 2000, a period predating widespread attention to potential increase in cardiovascular risk with second-generation antipsychotics. In our sample, physicians most likely prescribed the antipsychotics regardless of preexisting cardiovascular-related risk. Additionally, in data from a subpopulation of the study, we found no differences between the clozapine and risperidone groups in global functioning scores, substance abuse prevalence, and weight. We did find higher rates of smoking in the clozapine group, suggesting that the clozapine group may be at higher risk for CVD since smoking is a known risk factor. We do not know, however, which subjects were considered treatment refractory and whether cardiovascular risk differs by stage of the illness. Our study offers a significant strength over previous database studies, as we used chart diagnoses and treatment records as opposed to billing records and *ICD-10* codes to determine psychiatric diagnoses and drug treatment. Nonetheless, we identified cases by index treatment, and follow-up treatments were not recorded. As up to 70% of people with schizophrenia are known to switch their antipsychotic treatment within 1 year, many antipsychotic switches may have occurred during the follow-up period. Any patient who ever received clozapine in the state of Maryland was excluded from the risperidone group. Due

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to undetected medication switches, the risperidone group, although selected for initial treatment with risperidone, likely more broadly reflects mortality among patients with chronic schizophrenia who have never received clozapine.

The current study requires replication in other populations; however, it suggests that clozapine remains a useful option for treatment-resistant patients with schizophrenia, particularly under 55 years of age. Underuse of clozapine in treatment-resistant patients may be, in part, due to concern over its metabolic effects and the risk of greater mortality. This study in no way discounts the importance of limiting weight gain and metabolic side effects but suggests that switching antipsychotics[6] may not be the most urgent measure to address these concerns and that the risk-benefit profile of clozapine should be reevaluated. More effort should focus on diet, smoking, exercise, and lifestyle choices, as well as acting at the health system level to improve quality of medical care in people with mental disorders, in order to decrease the risk of cardiovascular disease mortality.

Drug names: clozapine (Fazaclo, Clozaril, and others), olanzapine (Zyprexa and others), quetiapine (Seroquel), risperidone (Risperdal and others).

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