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Clozapine, Diabetes Mellitus, Cardiovascular Risk and Mortality: Results of a 21-Year Naturalistic Study in Patients with Schizophrenia and Schizoaffective Disorder

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Abstract

The goal of this 21-year naturalistic study of clozapine-treated patients was to examine the cardiovascular risk factors following clozapine initiation and resultant mortality estimates from cardiovascular disease. Data were collected from January 1992 to February 2012 medical records from clozapine-treated patients with schizophrenia or schizoaffective disorder. Demographics, clozapine dosage and laboratory results were extracted at 12-month intervals. At clozapine initiation, the mean age of the 96 patients was 36.4 years±7.6 years; n=27 (28%) were women. The mean duration of clozapine use was 13 years. The Kaplan-Meier estimate for 21-year cardiovascular events was 29%, while the Kaplan-Meier estimate for 21-year mortality from cardiovascular disease was 10%. The mean cardiovascular risk increased during the first ten years ($p<.01$), while a slight decrease occurred beyond ten years ($p<.01$). Patients involved in cardiometabolic research showed a greater decrease in cardiovascular risk factors over 21 years ($p=.05$). The Kaplan-Meier estimate for 21-year all-cause mortality was 22%. Forty-one patients were diagnosed with diabetes (42.7%), compared to a nationwide prevalence of 13.7% in a similar age group. These results support the hypothesis that clozapine-treated patients are at risk for cardiovascular events and death secondary to an increased risk of medical disorders. Interventions that target weight loss, smoking cessation, and lipid profile improvement may alleviate the increased risk of cardiovascular mortality.

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Conflict of Interests

None declared.

Keywords

Clozapine; Schizophrenia; Cardiovascular Risk; Diabetes; Mortality

Introduction

High rates of medical morbidity and increased risk of mortality have long been associated with schizophrenia, with a life expectancy that is reduced by 15–25 years (1–3). Schizophrenia has been associated with an increased risk of cardiovascular disease (4–7), and the metabolic risk factors associated with antipsychotics are of growing concern. A countrywide study in Denmark showed that while the mortality from heart disease decreased in the general population between 1994 and 2006, mortality from heart disease actually increased in patients with schizophrenia (8). Clozapine remains the treatment of choice for treatment-resistant schizophrenia, but there is growing concern related to the increased risk of weight gain, metabolic syndrome, and cardiotoxicity associated with its use.

Patients with schizophrenia have higher rates of obesity (9). Weight gain is a well-known side effect of antipsychotic treatment (10, 11). Clozapine, together with olanzapine, has the greatest potential to induce weight gain in patients with schizophrenia treated with antipsychotic medications (12, 13). In our five-year naturalistic study, we found that weight gain with clozapine did not plateau until the fourth year (14). In our 10-year naturalistic study we found that some patients experienced a second period of weight gain that occurred when they improved enough to leave structured environments, such as residential settings, to move to independent apartments. Results from this study showed an increased risk of cardiovascular mortality associated with increased BMI over time (15).

Obesity is a risk factor for the development of type 2 diabetes. There is an increased risk for type 2 diabetes in people with schizophrenia both before (16) and after exposure to antipsychotic drugs (17, 18). In our 10-year cohort study we found that thirty-three out of ninety-six patients on clozapine had developed diabetes mellitus; increased BMI, total cholesterol level, and triglyceride levels were risk factors (15). A recent study of adults with psychosis in Australia showed that clozapine was a risk factor for type 2 diabetes, but not after adjusting for other predictors of diabetes including body mass index and hypercholesterolemia (19). Reducing body weight and improving lipid profiles have been a focus of recent efforts to reduce the cardiovascular risk and improve the physical health of those with serious mental illness (20, 21).

Despite known differences in risk profiles for weight gain and metabolic side effects in patients treated with clozapine, an increased risk of cardiovascular disease has not been clearly established compared to patients treated with more weight-neutral antipsychotics. In an autopsy study of patients with schizophrenia, no difference was found in cardiac-related measures (atherosclerosis, fibrosis, and hypertrophy) between those treated with clozapine and those treated with risperidone (22). A large retrospective cohort study of 1,084 patients found that cardiovascular mortality in schizophrenia did not differ between clozapine and risperidone (23). However, in this same cohort there was a trend toward higher

cardiovascular mortality with clozapine in patients who started antipsychotic treatment at an older age (>55) (23).

The goal of this 21-year naturalistic study of clozapine-treated patients was to examine the change in cardiovascular risk factors following clozapine initiation and resultant mortality estimates from cardiovascular disease.

Methods

Following institutional review board approval, records of 96 patients with schizophrenia or schizoaffective disorder (*DSM-IV* criteria) who had been treated with clozapine for up to 21 years from January 1992 to February 2012 at the Freedom Trail Clozapine Clinic were reviewed for known cardiovascular risk factors (24). Patients were excluded if they were treated with clozapine prior to joining the clinic and if their baseline data could not be obtained. Patients in the dataset were numbered 1–100. Only 96 patients had data (66 patients with schizophrenia and 30 patients with schizoaffective disorder). Cardiovascular risk was tabulated using known risk factors for cardiac heart disease (24) according to the following criteria: race (African American, Hispanic/Latino American, Asian American)=1 point; BMI ≥27 kg/m^2=1 point; hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg)=1 point; diabetes mellitus=1 point; cigarette smoking=1 point; history of left ventricular hypertrophy, myocardial infarction, or cerebrovascular accident=1 point; total cholesterol level ≥200 mg/dL or serum triglyceride level ≥150 mg/dL=1 point; and male gender=1 point (24). This is the same risk assessment used in our five-year (14) and ten-year (15) studies. Cardiovascular risk factors were tabulated at 1-year intervals over a 21-year period.

Autopsy reports and all medical records were reviewed by a research psychiatrist (D.C.H.) to determine the cause of death. When cardiovascular disease was identified, all records were carefully reviewed to determine if any evidence of clozapine-associated myocarditis or cardiomyopathy was present prior to the death such as persistent tachycardia, left ventricular hypertrophy, a prolonged corrected QT interval, eosinophilia, dyspnea on exertion, exercise intolerance, or edema. Patients with cerebrovascular accidents, myocardial infarctions, and symptomatic left ventricular hypertrophy were considered to have cardiovascular disease. This definition of cardiovascular disease was determined prior to study initiation.

Statistical Analysis

Baseline demographic and clinical characteristics were calculated for the sample. We then summarized the cardiovascular and metabolic events and related clinical characteristics that occurred in the sample over the 21-year follow-up period including the type of cardiovascular event, incidence of diabetes mellitus after clozapine initiation, and other demographic and clinical characteristics of these cases. Time to development of diabetes mellitus, cardiovascular disease, cardiovascular-related mortality and all-cause mortality associated with clozapine treatment at 12-month intervals over a 21-year period was calculated using Kaplan-Meier survival functions in Stata, Version 14.

To explore risk factor trajectories, we constructed mixed-effects models with a random intercept and slope for each patient as well as a fixed effect of time (in months) on the risk factors of interest: BMI, cardiovascular risk score, diabetes risk, weight, serum cholesterol level, serum triglyceride level and smoking status. The fixed effect estimates the mean trajectory of the change from baseline, and the random effects allow a separate trajectory for each patient. We then constructed a piecewise linear mixed-effect model to examine the difference in slope during the 2nd 10-year interval as compared to the first 10 years as reported in Henderson et al. (2005) (15). A plot of the mean number of cardiovascular risk factors and standard errors at each time point was produced using Stata, Version 14. We also evaluated whether research participation would moderate the trajectories of the aforementioned cardiovascular and metabolic risk factors over time by adding the main effect of research participation and an interaction term (research participation x time) to these longitudinal mixed-effect models.

Cox proportional hazards models were used to test the association between the aforementioned risk factors as well as key demographic characteristics and the development of the events of interest (incidence of diabetes, cardiovascular disease, cardiovascular-related mortality, all-cause mortality). Age, race, and sex were analyzed as fixed covariates, and BMI, total cholesterol level, clozapine total daily dose, serum triglyceride level, smoking status and weight were analyzed as time-varying covariates. Each covariate was analyzed separately. Time was used as the stratum and ties were handled using the exact partial likelihood method. All p-values are 2-tailed, and a p-value of .05 was considered evidence of statistical significance.

Results

Characteristics of the Sample

Baseline demographic and laboratory measures are presented in Table 1. Sixty-nine subjects (72%) were men and 27 (28%) were women. The mean age at clozapine initiation was 36.4±7.6 years; six subjects (6%) were African Americans, four (4%) were Hispanic Americans, and one (1%) was an Asian American. The mean length of treatment with clozapine was 13 years (mean 150.3 months; SD 68.1 months) ranging from 6–246 months. Some subjects initiated clozapine after their first assessment, while three discontinued early. Deaths also contributed to a shorter mean duration of clozapine treatment.

Time To Development of Diabetes Mellitus, Cardiovascular Disease, Cause-Specific (Cardiovascular-Related) Mortality and All-Cause Mortality

Diabetes Mellitus—Forty-one patients were diagnosed with diabetes (42.7%) over the 21-year period. Thirty-three patients were diagnosed within 10 years of clozapine initiation, with an additional 8 diagnosed during the 10–21 year follow-up period. The probability of remaining diabetes free at the 10- and 21-year follow-up was 0.63 and 0.50, respectively (see Figure 1a; Table 2).

Cardiovascular Disease and Related Mortality—There were 17 cardiovascular events experienced by 15 patients (2 patients experienced 2 events each) during the 21-year

period (see Table 3), with 4 of them occurring in the second decade. The Kaplan-Meier estimate for surviving without a cardiovascular event over the 10- and 21-year period was 0.86 and 0.81, respectively (see Figure 1b; Table 2). The Kaplan-Meier survival estimates for 10- and 21-year mortality from cardiovascular disease were 0.92 and 0.90, respectively (see Figure 1c; Table 2). One patient died secondary to a cardiovascular event in the second decade, while there were 7 cardiovascular deaths in the first decade after clozapine initiation.

All-Cause Mortality—The probability of survival was 0.87 and 0.78 at 10 and 21 years, respectively (see Figure 1d; Table 2). The majority of deaths occurred during the first decade (n=11) as compared to the second decade (n=5). Five patients, ages 47–54, died from cancer-related causes, two of which were lung cancer related. The remaining causes of death included cardiovascular disease (n=8), perforated bowel (n=1) and unknown causes (n=2).

Cardiovascular and Metabolic Risk Trajectories

There was a significant increase in weight, BMI, diabetes risk and cardiovascular risk factors over the 21-year period, and an overall decrease in cholesterol levels ($p<.001$). While there was no significant overall change in serum triglyceride levels over the 21-year period, there was a significant decrease in triglyceride levels during the 2nd decade (linear coefficient of −1.1 mg/dL/month, SE=0.423, $p=0.007$). Results from the piecewise linear models suggest that the increases in cardiovascular risk (see Figure 2), cholesterol, triglycerides and weight were significantly attenuated during the 2nd decade relative to the first decade of the study. Probability of smoking did not change over time (see Table 4). Patients who were involved in metabolic research studies showed a decrease in cardiovascular risk factors, including decreased cholesterol ($p=0.049$), triglycerides ($p=0.007$) and weight ($p=0.057$) over a 21-year period compared to those who were not involved in research.

Association Between Demographic and Cardiometabolic Risk Factors and Incidence of Diabetes, Cardiovascular Disease, Cardiovascular-Related Mortality and All-Cause Mortality

Demographic factors (age, sex and race) were not related to cardiovascular events, cardiovascular-related mortality or all-cause mortality. As compared to Caucasians, African Americans (HR=11.4, 95% CI: 3.6, 36.4) and Hispanics (HR=3.7, 95% CI: 1.0, 13.2) were more likely to develop diabetes mellitus over the follow-up period. Moreover, the hazard of diabetes was also greater for individuals with higher body mass index (BMI; HR=1.11, 95% CI: 1.1, 1.2). Lastly, having diabetes mellitus was associated with experiencing a cardiovascular event (HR=3.8, 95% CI: 1.3, 11.4) and all-cause mortality (HR=3.94, 95% CI: 1.2, 13.0). All other cardiometabolic risk factors (cholesterol, triglycerides, blood pressure, clozapine dose, smoking status) were not significantly associated with the events of interest. See Table 5.

Discussion

Clozapine is the only antipsychotic medication approved for treatment-resistant schizophrenia, but its use is often limited due to its adverse cardiometabolic risk profile. In addition to the low risk of myocarditis and cardiomyopathy (25, 26), clozapine is known to

induce weight gain and may contribute to the risk of developing diabetes mellitus and other metabolic abnormalities (27–29). These risks are of particular concern in a population that is already predisposed to cardiovascular disease (30, 31) and metabolic dysfunction (32, 33).

Our results support the hypothesis that clozapine-treated patients are at risk for cardiovascular events and death secondary to clozapine-associated medical disorders such as obesity, diabetes, and hyperlipidemia. Fifteen of the 96 patients in our cohort (15.6%) experienced a cardiovascular event over a 21-year period, with eight patients dying from a cardiac event. While data on the 21-year risk of cardiovascular events in a healthy population of the same age are not available, the 30-year risk of a cardiovascular event in patients age 20–29 is 2.5% for women and 5% for men (34). A significant increase in BMI, weight, and cardiovascular risk factors was seen over the 21-year period. Forty-three percent of patients were diagnosed with diabetes mellitus—far more than would be expected based on the nationwide prevalence of 13.7% in those ages 45–64 (35).

Most of the risk for cardiovascular morbidity and mortality was engendered during the first decade of our study. Increased BMI, cardiovascular risk, triglycerides, and weight seen during the first 10 years were significantly attenuated during the second decade. There was, in fact, a *decrease* in cardiovascular risk factors in the second decade. This was paralleled by lower rates of cardiovascular events and death. The probability of smoking remained relatively consistent over the 21-year period. While rates of smoking in schizophrenia are known to be 2–3 times higher than the general population (36), risk of tobacco use is lower in patients treated with clozapine (37). Our data set did not include quantity of tobacco use within the subset of patients who smoked, but there is evidence that smokers decrease their daily use of cigarettes after clozapine initiation (38).

The reason for the decline in rates of cardiovascular morbidity, mortality, and risk factors in the second decade relative to the first is likely multifactorial. The rapid weight gain seen within the first three months of treatment with clozapine has been reported to increase at a slower rate for a year or longer and eventually plateau (39, 40). In our cohort, we observed an increase in weight during the first decade that was associated with the development of diabetes mellitus and cardiovascular mortality, followed by a leveling off of BMI during the second decade. Additionally, clinicians have become increasingly vigilant for the cardiometabolic side effects of antipsychotic medication during recent years. Patients who were enrolled in metabolic research studies in our cohort had a decrease in cardiovascular risk factors compared to those who were not. These patients were often enrolled in studies that included dietary and lifestyle interventions and were seen by clinicians regularly. While it is possible that there were baseline differences between these groups—including functional status and disease severity—the only difference in cardiovascular disease risk factors between the groups was a higher baseline cholesterol level in the research group.

The number of cancer-related deaths in our sample was alarming. Five patients, ages 48–54, passed away from cancer. Two of these patients had lung cancer and three of these patients had widely metastatic disease of unknown source. Population-based studies from several countries have shown that individuals with schizophrenia are 1.5 to 2 times more likely to die of cancer than patients without mental illness (41–43). Contributing factors at the level

of the patient, the provider, and the healthcare system likely influence this increase in mortality (44). In a large Swedish study, cancer mortality in schizophrenia patients was primarily explained by under detection—despite the fact that these patients had increased contacts with the healthcare system (41). The relationship between antipsychotic use and cancer has not been examined, though antipsychotic continuity has been associated with overall decreased mortality (45).

There are several limitations to the current study. First, it is possible that other unknown factors affected the rates of cardiovascular events and development of diabetes mellitus. These include family history, diet and exercise habits, and frequency of healthcare screening. In addition, there are measures that are now known to be associated with increased cardiovascular risk, including low HDL cholesterol, and measures known to be associated with increased metabolic risk, including increased waist circumference, which were not included in our database as they were not recognized as major risk factors when data collection was started. Many patients participated in interventions that may have reduced the overall incidence of new-onset diabetes or cardiovascular death in this cohort. Finally, although medical records and autopsy reports were carefully reviewed, it is possible that undetected cardiomyopathy or myocarditis contributed to the cardiovascular deaths.

Schizophrenia is associated with high rates of medical comorbidity and mortality associated with cardiovascular disease and metabolic dysfunction, and this risk may be compounded by the use of atypical antipsychotic medications including clozapine. An increased risk of cardiovascular events, mortality, and development of diabetes was seen in this cohort of patients over a 21-year period. This risk was highest in the first decade. Screening and interventions that target weight loss, smoking cessation, and lipid profile improvement may mitigate the increased risk of cardiovascular morbidity and mortality associated with clozapine use. Increased vigilance with regards to cancer screening and detection is necessary for this high-risk population.

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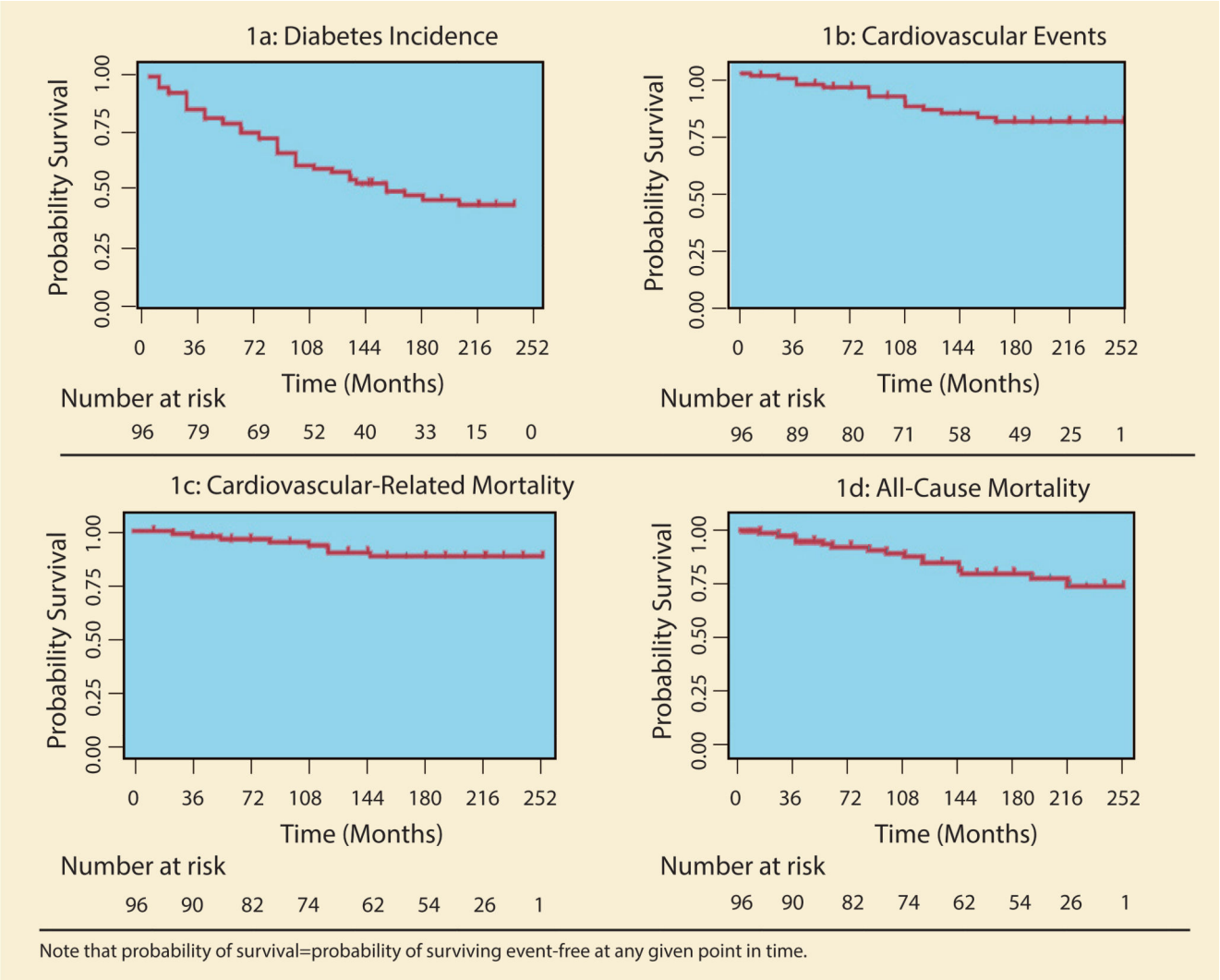

Figure 1. Time to Diabetes Incidence, Cardiovascular Events, Cardiovascular-Related Mortality, and All-Cause Mortality

Note that probability of survival=probability of surviving event-free at any given point in time.

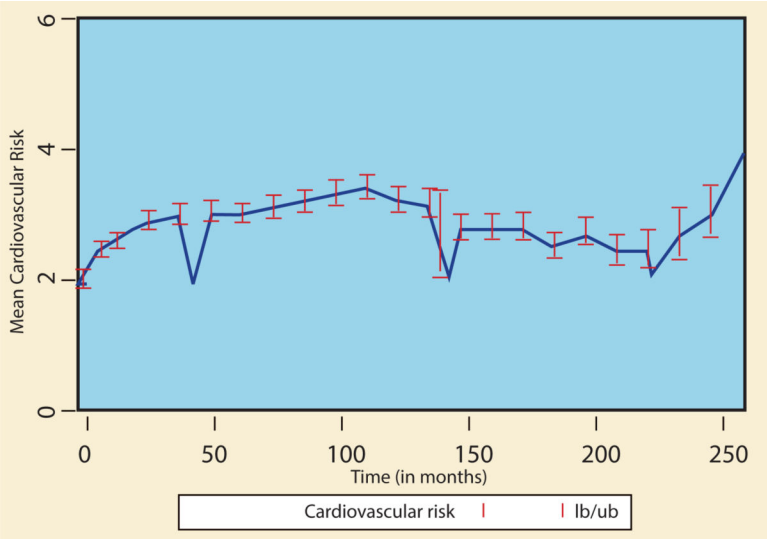

Figure 2.
Mean Cardiovascular Risk (±SE) for 96 Patients on Clozapine

Table 1

Demographic Characteristics and Baseline Values for 96 Patients with Schizophrenia Treated with Clozapine Over a 21-Year Period

Variable	N (%)	Mean (SD)
Age		36.4 (7.6)
Gender		
Male	69 (72)	
Female	27 (28)	
Race		
White	85 (89)	
African American	6 (6)	
Hispanic American	4 (4)	
Asian American	1 (1)	
Diagnosis		
Schizophrenia	66 (69)	
Schizoaffective disorder	30 (31)	
Smoking status		
Smoker	61 (63.5)	
Nonsmoker	35 (36.5)	
Baseline measures		
Weight, lb		174.2 (35.5)
Body mass index, kg/m^2		27.3 (5.2)
Glucose level, mg/dL		93 (12)
Blood pressure, mmHg		
Systolic		114 (13)
Diastolic		76 (9)
Total cholesterol level, mg/dL		196 (47)
Serum triglyceride level, mg/dL		180 (136)
Cardiovascular risk factors		2.0

Cardiovascular risk was tabulated using the following criteria: race (African American, Hispanic/Latino American, Asian American)=1 point; BMI ≥27 kg/m^2=1 point; hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg)=1 point; diabetes mellitus=1 point; cigarette smoking=1 point; history of left ventricular hypertrophy, myocardial infarction, or cerebrovascular accident=1 point; total cholesterol level ≥200 mg/dL or serum triglyceride level ≥150 mg/dL=1 point; and male gender=1 point.

Table 2

Survival Functions for Events of Interest (N=96)

	Probability of Survival (Event-Free)		Number of Events	
Event	**10-Year**	**21-Year**	**10-Year**	**21-Year**
Incident Diabetes Mellitus	0.630	0.503	33	8
Cardiovascular Event	0.858	0.811	12	3
Cardiovascular-Related Mortality	0.915	0.899	7	1
All-Cause Mortality	0.873	0.782	11	5

Table 3

Cardiovascular Events Over a 21-Year Period in Clozapine-Treated Patients

Patient No. in Dataset	Patient Not in 10-Yr Paper	Duration of Clozapine Treatment, Months	*ICD-9* Diagnosis	Gender	Cardiovascular Event	Race	Age at Time of Event, Year	Clozapine Dose (mg/d)	BMI (kg/m^2)	Diabetes after Clozapine Initiation	Smoking Status
5	1	36	295.3	Male	Non-fatal MI	White	50	525	26.48	No	Yes
5		146	295.3	Male	Fatal MI	White	57				
8		132	295.7	Male	Non-fatal CVA	White	37	500	36	Yes	
9	11	84	295.9	Male	Non-fatal CVA	White	45	400	17	Yes	Yes
18		54	295.3	Female	Fatal CVD	White	59				
19	2	108	295.9	Male	Non-fatal MI	White	49	450	35	Yes	Yes
23		108	295.3	Female	Non-fatal LVH	White	50	500		No	Yes
23	6	120	295.3	Female	Fatal MI	White	51	500	51	No	Yes
26		84	295.3	Male	Fatal MI	White	50	550	26	No	Yes
30		156	295.7	Male	Non-fatal MI	White	63	500	26	No	Yes
35		6	295.3	Male	Non-fatal LVH	White	27	400	27	No	No
37		36	295.3	Female	Fatal CVD	White	45	125	31	Yes	Yes
70		160	295.7	Female	Non-fatal LVH	White	38	550	35	Yes	No
75	8	108	295.7	Male	Fatal CVD	Hispanic	29		43	Yes	Yes
79	4	24	295.3	Female	Fatal CVD	African American	26	175	39	Yes	No
94		120	295.3	Male	Fatal MI	White	49		27	No	Yes
98	3	84	295.1	Female	Non-fatal MI	White	42	350	29	No	Yes

ICD: International classification of diseases; 295.1: disorganized type schizophrenia; 295.3: paranoid type schizophrenia; 295.7: schizoaffective disorder; 295.9: unspecified schizophrenia; BMI: Body Mass Index; CVA: cerebrovascular accident; CVD: MI cardiovascular disease; MI: myocardial infarction; LVH: left ventricular hypertrophy; MVI: multivitamin.

Table 4

The Effect of Time (Slope) on CVD and Metabolic Risk Factors

DV:	Months 0–120				Months 121–252				Months 0–252			
	B	SE	z	p	B	SE	z	p	B	SE	z	p
BMI *	0.027	0.004	6.73	<.001	−0.011	0.006	−1.87	0.061	0.018	0.004	4.69	<.001
Cardiovascular Risk *	0.009	0.001	8.67	<.001	−0.009	0.001	−6.19	<.001	0.004	0.001	3.88	<.001
Cholesterol	−0.152	0.052	−2.93	0.003	−0.348	0.128	−2.71	0.007	−0.188	0.044	−4.26	<.001
Diabetes Risk	0.012	0.001	10.27	<.001	0.009	0.012	0.74	0.456	0.012	0.001	10.36	<.001
Triglycerides *	0.195	0.167	1.17	0.241	−1.143	0.423	−2.70	0.007	−0.102	0.121	−0.84	0.399
Weight *	0.169	0.025	6.64	0.000	−0.082	0.038	−2.15	0.032	0.110	0.024	4.57	0.000
Smoking Status (Y/N)	−0.001	0.002	−0.95	0.344	0.004	0.004	1.09	0.274	0.001	0.002	0.33	0.745

Cardiovascular risk was tabulated using the following criteria: race (African American, Hispanic/Latino American, Asian American)=1 point; BMI ≥27 kg/m^2=1 point; hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg)=1 point; diabetes mellitus=1 point; cigarette smoking=1 point; history of left ventricular hypertrophy, myocardial infarction or cerebrovascular accident=1 point; total cholesterol level ≥200 mg/dL or serum triglyceride level ≥150 mg/dL=1 point; and male gender=1 point.

* Effect of time (slope) is significantly different between the first and second decade.

Table 5

Hazard of Experiencing Events of Interest During the 21-Year Follow-Up Period by Demographic and Clinical Covariates

	Diabetes Incidence			Cardiovascular Events			Cardiovascular-Related Mortality			All-Cause Mortality		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Age (in years)	1.01	0.97, 1.05	0.660	1.00	0.93, 1.07	0.957	1.03	0.93, 1.14	0.571	1.07	0.99, 1.15	0.090
African American (ref: White)	11.44	3.59, 36.39	0.000	1.33	0.17, 10.36	0.784	2.92	0.35, 24.54	0.323	2.99	0.66, 13.48	0.155
Hispanic (ref: White)	3.69	1.03, 13.15	0.044	2.02	0.26, 16.00	0.504	5.01	0.59, 42.91	0.141	2.25	0.29, 17.53	0.437
Male	1.08	0.54, 2.18	0.829	0.77	0.26, 2.28	0.642	0.36	0.09, 1.46	0.155	0.48	0.18, 1.30	0.150
BMI	1.11	1.05, 1.18	0.000	0.98	0.89, 1.07	0.594	1.14	1.00, 1.29	0.051	1.04	0.95, 1.15	0.397
Cholesterol	1.00	0.99, 1.01	0.882	1.00	0.98, 1.01	0.692	1.00	0.96, 1.03	0.756	0.99	0.98, 1.01	0.314
Triglycerides	1.00	1.00, 1.00	0.073	0.99	0.99, 1.00	0.242	1.00	0.99, 1.01	0.685	1.00	1.00, 1.00	0.826
Systolic Blood Pressure	1.01	0.99, 1.04	0.245	1.01	0.97, 1.05	0.619	1.02	0.97, 1.08	0.353	1.02	0.98, 1.07	0.292
Diastolic Blood Pressure	1.01	0.98, 1.05	0.536	1.02	0.96, 1.07	0.590	1.09	1.00, 1.18	0.059	1.07	1.00, 1.14	0.067
Clozapine Dose	1.00	1.00, 1.00	0.696	1.00	1.00, 1.00	0.889	1.00	0.99, 1.00	0.247	1.00	0.99, 1.00	0.222
Smoking Status	1.20	0.61, 2.36	0.597	1.92	0.52, 7.04	0.324	2.97	0.35, 25.55	0.321	1.10	0.33, 3.68	0.875
Diabetes Mellitus	--	--	--	3.78	1.26, 11.36	0.018	3.85	0.75, 19.92	0.108	3.94	1.20, 12.96	0.024

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