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Antipsychotic effects on estimated 10-year coronary heart disease risk in the CATIE schizophrenia study

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Abstract

Objective: Persons with schizophrenia die earlier than the general population, in large part due to cardiovascular disease. The study objective was to examine effects of different antipsychotic treatments on estimates of 10-year coronary heart disease (CHD) risk calculated by the Framingham Heart Study formula.
Method: Change in 10-year risk for CHD was compared between treatment groups in 1125 patients followed for 18 months or until treatment discontinuation in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial.
Results: The covariate-adjusted mean change in 10-year CHD risk differed significantly between treatments. Olanzapine was associated with a 0.5% (SE 0.3) increase and quetiapine, a 0.3% (SE 0.3) increase; whereas risk decreased in patients treated with perphenazine, −0.5% (SE 0.3), risperidone, −0.6% (SE 0.3), and ziprasidone −0.6% (SE 0.4). The difference in 10-year CHD risk between olanzapine and risperidone was statistically significant ($p=0.004$). Differences in estimated 10-year CHD risk between drugs were most marked in the tertile of subjects with a baseline CHD risk of at least 10%. Among individual CHD risk factors

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used in the Framingham formula, only total and HDL cholesterol levels differed between treatments.
Conclusions: These results indicate that the impact on 10-year CHD risk differs significantly between antipsychotic agents, with olanzapine producing the largest elevation in CHD risk of the agents studied in CATIE.

Keywords: Schizophrenia; Antipsychotic; Coronary heart disease risk; Blood pressure; Cholesterol

1. Introduction

Persons with schizophrenia have increased death rates, with standardized mortality ratios up to three times those for the general population (Felker et al., 1996; Brown, 1997). While most studies report elevated risks for suicide and accidental death, more recent work suggests much premature mortality may be due to cardiovascular disease (Osby et al., 2000; Colton et al., 2006).

People with schizophrenia have a higher prevalence of most traditional factors contributing to elevated coronary heart disease (CHD) risk. Smoking rates, in particular, are much higher than the general population (Goff et al., 1992; Lohr and Flynn, 1992). Unhealthy diet and physical inactivity also appear increased and contribute to the high prevalence of obesity (Daumit et al., 2003; McCreadie, 2003; Strassnig et al., 2003; Daumit et al., 2005; Brown et al., 2006). In large part stemming from obesity, the increased risk for diabetes mellitus in schizophrenia also is well known. Recent published baseline data from the CATIE Trial provide evidence that hypertension and low HDL cholesterol are more prevalent in patients with schizophrenia than the general population (Goff et al., 2005; McEvoy et al., 2005).

Although elevation in CHD risk factors is due in part to unhealthy lifestyles and lower quality primary care in people with schizophrenia, atypical antipsychotics likely contribute substantially to increasing CHD risk factors through effects on weight gain, glucose dysregulation and lipid abnormalities (Allison et al., 1999; Meyer and Koro, 2004; Kreyenbuhl et al., 2006; Newcomer and Haupt, 2006). Extensive use of these agents has raised important concerns about cardiovascular health for populations using these medications chronically (Marder et al., 2004).

The Framingham risk equation, derived from the Framingham Heart Study and Framingham Offspring Study cohorts, provides a validated calculation of 10-year risk of CHD, including angina, myocardial infarction and cardiac death, tested in a variety of populations (Wilson et al., 1998; D'Agostino, 2001). Using baseline assessments of schizophrenia patients in CATIE, we documented a significant elevation in 10-year CHD risk compared to age, race and gender-matched controls from the National Health and Nutrition Examination Survey (NHANES) (Goff et al., 2005). Schizophrenia patients had higher rates of smoking, diabetes, hypertension and lower HDL cholesterol levels.

Despite evidence that certain atypical antipsychotics predispose to weight gain, glucose and lipid abnormalities, the effect of individual antipsychotics on overall CHD risk over time has not been characterized previously. This is an important factor in evaluating risks vs. benefits of treatment and a crucial public health issue for patients with schizophrenia and others using these medications (American Diabetes Association and American Psychiatric Association, 2004). Phase 1 of the CATIE Schizophrenia Trial provides a unique opportunity to examine this critical question. Thus, the study objective was to assess the effect of specific antipsychotics on estimates of 10-year coronary heart disease risk in patients with schizophrenia. We hypothesized there would be a differential CHD risk associated with the various drugs used in CATIE participants and that changes in total and HDL cholesterol, hypertension and diabetes would vary by treatment.

2. Methods

2.1. Study setting and design

The CATIE Schizophrenia Study was conducted between January 2001 and December 2004 at 57 U.S. sites and included an algorithmically determined series of treatment phases (Stroup et al., 2003). A total of 1460 patients were randomized to receive olanzapine, perphenazine, quetiapine, or risperidone under double-blind conditions and followed for up to 18 months or until initial treatment discontinuation. Two hundred thirty-one patients with tardive dyskinesia (TD) were excluded from assignment to perphenazine; ziprasidone was added to the study in 2002. Randomization thus took place under four strata within which patients had an equal chance of being randomly assigned to treatments:

TD patients pre-ziprasidone (randomized to olanzapine, quetiapine, or risperidone), non-TD patients pre-ziprasidone (randomized to olanzapine, quetiapine, risperidone or perphenazine), and these two groups in the cohort of patients after ziprasidone was added. Patients whose assigned treatment was discontinued could receive other treatments in phases 2 and 3. This analysis reports on phase 1 results.

2.2. Study population

An IRB at each site approved the study. Participants were outpatients with schizophrenia diagnosed by a research psychiatrist using a modified SCID interview and were between 18 and 65 years old. After complete description of the study to the subjects, written informed consent was obtained. The analysis population consists of 1460 patients randomized in the CATIE study. Of these, 10-year CHD risk was calculable at baseline and end of phase 1 for 1125 patients. We also performed an analysis restricted to subjects with fasting blood samples at baseline and 3 months for a more sensitive and uniform risk factor assessment. This analysis was limited to 283 subjects, of whom change in 10-year CHD risk was calculable for 270. Results were generally consistent with study population results, although harder to interpret due to small sample sizes. They are included in Appendix A.

2.3. Measures

During comprehensive medical evaluations patients were asked about current medications, cigarette smoking and whether they had been diagnosed or treated for hypertension or diabetes. Vital signs, weight and smoking status were collected at screening, months 1, 3, 6, 9, 12, 15, 18 and end of phase 1 (up to 18 months). Patients were instructed to fast overnight to measure serum glucose, total cholesterol and HDL cholesterol. Laboratory measures were collected at baseline, months 3, 6, 12, 18, and end of phase and were considered fasting if ≥ 8 h after ingesting food or calorie containing beverages.

2.4. Primary outcome

The primary outcome was change in 10-year CHD risk using the Framingham Heart Study formula by Wilson et al. (1998). Inputs to this formula include age, total and HDL cholesterol (mg/dl), blood pressure stage (Fifth Joint National Committee (JNC-V)) (Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure, 1993), presence of diabetes mellitus and presence of smoking. Separate prediction models are used for men and women. The formula reports the average risk (percent) of developing CHD over a 10-year period. Changes in CHD risk are reported here as absolute changes in risk estimates between end of phase and baseline. For example, if a person with baseline risk of 9.0% had an increase of 0.8%, this corresponds to a new CHD risk of 9.8%. All calculations use baseline age so changes in CHD risk reflect risk factors other than aging.

2.5. Secondary outcomes

Secondary outcomes were changes in diabetes, smoking status, hypertension, total cholesterol and HDL by antipsychotic treatment. We classified participants as having diabetes mellitus at baseline if they had a fasting glucose of ≥ 126 mg/dl, random glucose of ≥ 200 mg/dl, current use of oral hypoglycemics or insulin, or a medical history of diabetes. At follow-up, we classified participants with diabetes if they met baseline criteria or any of the following during follow-up: new oral hypoglycemic medications or insulin; fasting glucose of ≥ 126 mg/dl; random glucose of ≥ 200 mg/dl or new diagnosis of diabetes recorded.

Participants had hypertension at baseline if they had a systolic blood pressure of ≥ 140 mm Hg, diastolic blood pressure of ≥ 90 mmHg or if they took an antihypertensive. At follow-up, participants were considered to have hypertension if they met blood pressure criteria at the end of phase visit or if they were taking antihypertensive medication either at baseline or during follow-up.

Patients were considered to be smokers at baseline or follow-up if they reported smoking five or more cigarettes daily over the previous week.

2.6. Statistical analyses

Treatment groups were compared for baseline values of the Framingham risk score, items contributing to its calculation, demographic characteristics, and phase 1 treatment duration with 4 degree of freedom (*df*) analysis of variance (ANOVA) or chi-squared tests.

For the primary analysis, unadjusted treatment means of the change from baseline in 10-year CHD risk at end of phase and at 3 months were compared using an ANOVA. If the overall 4 *df* test was significant at $p<0.05$, then the 10 treatment pairwise comparisons were made using Bonferroni correction to maintain the overall Type I error rate at 0.05, yielding an alpha of $0.05/10=0.005$. Due to the relatively conservative nature of this correction, p-values between 0.005 and 0.01 are also identified for the reader's discretion. Treatment comparisons were then refined by analysis of covariance (ANCOVA)

adjusting for baseline risk and phase 1 treatment duration, as well as demographic and other baseline measures found to be associated with change in CHD risk. CATIE study design factors for study entrance after ziprasidone treatment option was added, and for having TD at baseline were also evaluated for inclusion. Fasting status at baseline and end of phase 1 was also considered as a possible covariate. Age and gender were not covariates since they are used within the risk score calculation. Interactions between treatment group and significant covariates were explored, and for identified interactions, treatment groups were compared within levels of the covariate using additional ANCOVA models.

Treatment groups were compared for change from baseline in the secondary categorical outcomes of smoking status, diabetes, and hypertension by a mean-score chi-square test for ordinal data (4 *df*). Change from baseline in the secondary continuous outcome measures of HDL and total cholesterol was evaluated similar to the primary outcome. Age and gender were also considered as potential covariates in these ANCOVA models. The end of phase analyses of these outcomes were based on the subset of the 1460 randomized patients for whom those data were available for at least one follow-up visit. Similarly at 3 months, secondary outcomes were analyzed for the subset of the 283 patients fasting at baseline and 3 months with data available. In addition, change from baseline in the total and HDL cholesterol measurements collected at 3, 6, 12 and 18 months were compared across treatment groups with a mixed model including terms representing the baseline value of the dependent variable, time (treated as a classification variable), other covariates determined to be important in adjusted analyses, and terms representing baseline-by-time and treatment-by-time interactions. A random subject effect and a spatial power covariance structure were used to adjust standard errors for correlation of observations within-individual.

3. Results

3.1. Baseline participant characteristics

Table 1 depicts baseline demographics, cardiovascular risk factors and phase 1 treatment duration overall and by gender for the 1125 primary analysis participants, 839 males and 286 females, for whom change in 10-year CHD risk was available. The mean age was 40.7 (SD 11.1) years, and the sample was 75% male and 62% white. Twelve percent of the population had diabetes mellitus, 58% smoked cigarettes, and 34% had hypertension. Females' mean 10-year CHD risk was significantly lower than males, at 5.7% compared to 9.5%. Females' lower prevalence of cigarette smoking (50 vs. 61%) and higher HDL (47.1 vs. 42.0 mg/dl) contributed

Table 1
Baseline demographics, coronary heart disease risk factors, and duration of phase 1 treatment for CATIE subjects overall and by gender

	Overall (n=1125)	Males (n=839)	Females (n=286)
Age[a]	40.7±11.1	40.1±11.3	42.5±10.2
White[a, b]	701 (62)	543 (65)	158 (55)
Hispanic	133 (12)	98 (12)	35 (12)
Years of education[b]	12.1±2.2	12.2±2.2	12.1±2.5
Diabetes	139 (12)	100 (12)	39 (14)
Cigarette smoker[a]	657 (58)	515 (61)	142 (50)
Hypertension	377 (34)	294 (35)	83 (29)
BMI (kg/m^2)[a, b]	29.9±7.0	29.0±6.5	32.8±7.6
Total cholesterol (mg/dl)	202.2±47.5	201.2±47.5	205.1±47.4
High density cholesterol (mg/dl)[a]	43.3±13.4	42.0±13.1	47.1±13.8
10-year estimated CHD risk[a]			
Mean	8.5±7.4	9.5±7.5	5.7±6.3
<5%	444 (39)	272 (32)	172 (60)
5 to <10%	316 (28)	256 (31)	60 (21)
≥10%	365 (32)	311 (37)	54 (19)
Phase 1 treatment duration	9.5±7.0	9.6±7.1	9.1±6.9

Table entries are n (%) or Mean±SD.
Based on 1125 subjects for whom change in 10-year CHD risk could be calculated.
[a] Significantly different between males and females ($p<0.05$).
[b] Percentages are based on number of patients with data available. For whites, N=285 for females. For years of education: males, N=835; females, N=285. For BMI: males, N=832; females, N=283.

to this lower CHD risk. Although females had higher mean BMI (32.8 vs. 29.0 kg/m^2) than males, BMI is not included in the Framingham formula.

The baseline estimated 10-year CHD risk ranged from 8.1 to 9.1% across antipsychotic medications. Demographic characteristics, cardiac risk factors and estimates of 10-year cardiac risk were similar across treatment groups. Average phase 1 treatment duration was 9.5 months, ranging from 8.2 to 11.3 months across the groups ($p<0.001$). The Appendix Table 1 shows corresponding baseline measures for 270 participants with fasting serum values at baseline and 3 months for whom change in 10-year CHD risk was available.

3.2. Change in 10-year coronary heart disease risk estimates

The covariate-adjusted change in 10-year coronary heart disease risk estimate significantly differed between treatment groups ($p=0.007$) (Table 2). The risk estimates were highest for olanzapine then quetiapine and lowest for risperidone and ziprasidone followed by perphenazine. Individual comparisons between treatment groups revealed a significant difference between risperidone (−0.6, SE=0.3) and olanzapine (0.5, SE=0.3) ($p=0.004$). The Appendix Table 2 shows CHD risk results for participants with fasting serum values at baseline and 3 months. Although the sample sizes were substantially smaller, the adjusted 3-month change from baseline in 10-year risk was very similar to those at end of phase for olanzapine, quetiapine and risperidone. However, the 3-month analysis showed greater decrease for the perphenazine group compared to endpoint, and a deterioration rather than an improvement for ziprasidone.

3.3. Change in 10-year coronary heart disease risk estimates by baseline risk, age and gender

We identified an interaction between antipsychotic treatment assignment and CHD risk status at baseline, and report change in CHD risk for three baseline risk categories which approximate the tertiles (Fig. 1). The

Table 2
Change in 10-year coronary heart disease risk estimates in CATIE subjects from baseline to end of phase 1 by antipsychotic treatment group, age and gender

	Olanzapine	Perphenazine	Quetiapine	Risperidone	Ziprasidone	*p*-value
Overall (unadjusted)	0.5±4.4[a]	−0.6±4.3	0.3±4.4	−0.6±4.6[a]	−0.5±4.4	0.012
	(269)	(207)	(258)	(255)	(136)	
Overall (adjusted)[b]	0.5±0.3[c]	−0.5±0.3	0.3±0.3	−0.6±0.3[c]	−0.6±0.4	0.007
	(269)	(207)	(258)	(255)	(136)	
Age in years						
Under 40	0.4±0.2[d]	−0.5±0.2[d]	−0.1±0.2	0.0±0.2	−0.6±0.3[d]	0.016
	(109)	(86)	(107)	(104)	(63)	
40–49	0.2±0.5	0.5±0.5	0.3±0.5	−0.3±0.5	−0.8±0.7	NS
	(99)	(80)	(86)	(94)	(41)	
50 and older	1.1±0.7[e]	−2.0±0.9	0.6±0.7[f]	−2.2±0.8[e,f]	−0.4±1.0	0.008
	(61)	(41)	(65)	(57)	(32)	
Gender						
Males	0.6±0.3[g]	−0.7±0.4[g]	0.2±0.3	−0.6±0.3[g]	−0.7±0.4	0.017
	(192)	(158)	(196)	(194)	(99)	
Females	0.2±0.4	0.0±0.5	0.7±0.4	−0.6±0.4	−0.4±0.6	NS
	(77)	(49)	(62)	(61)	(37)	

Table entries are ANCOVA least squares adjusted Mean±SE, (*n*) except for first row (overall unadjusted results with Mean±SD, (*n*)). NS denotes non-significant, $p\geq 0.05$. Based on 1125 subjects for whom change in 10-year CHD risk could be calculated.

[a] Difference in risk numerically different for Olanzapine compared to Risperidone, but not statistically significant with Bonferroni correction ($p=0.008$).

[b] Model includes baseline risk, time to treatment discontinuation, and fasting status at baseline and end of phase 1.

[c] Difference in risk statistically significant with Bonferroni correction for Olanzapine compared to Risperidone ($p=0.004$).

[d] Difference in risk statistically significant with Bonferroni correction for Olanzapine compared to Perphenazine ($p=0.004$) and Ziprasidone ($p=0.004$).

[e] Difference in risk statistically significant with Bonferroni correction for Olanzapine compared to Risperidone ($p=0.002$).

[f] Difference in risk numerically different for Quetiapine compared to Risperidone, but not statistically significant with Bonferroni correction ($p=0.009$).

[g] Difference in risk numerically different for Olanzapine compared to Perphenazine ($p=0.007$) and Risperidone ($p=0.007$), but not statistically significant with Bonferroni correction.

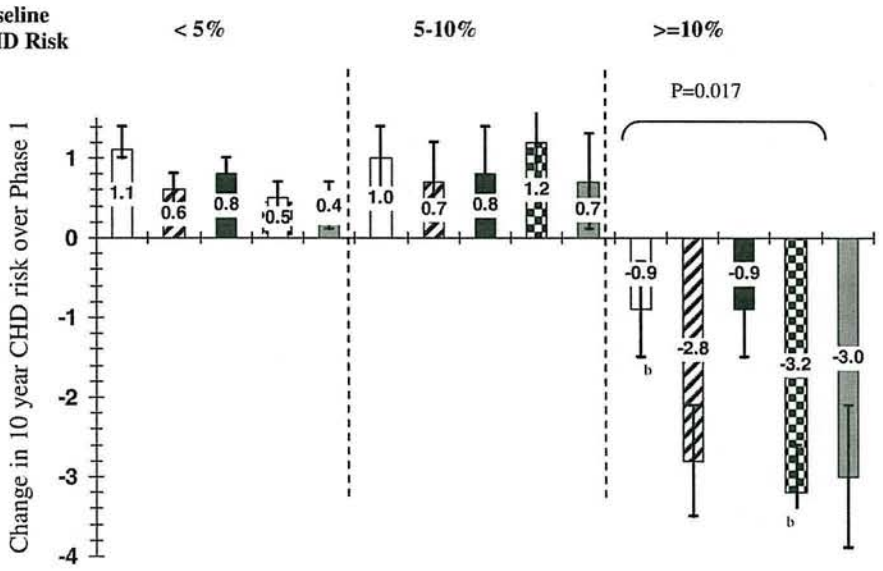

Fig. 1. Change in 10-year coronary heart disease (CHD) risk by Baseline CHD Risk Categories. ANCOVA least squares adjusted results with Mean +/− SE. Model includes baseline risk, time to treatment discontinuation, and fasting status at baseline and end of phase 1. [b]Difference in risk numerically different but not statistically significant with Bonferroni correction ($p=0.008$). □: Olanzapine, ▨: Perphenazine, ■: Quetiapine, ▩: Risperidone, ▤: Ziprasidone.

covariate-adjusted change in 10-year cardiac risk was significantly different across the five treatment arms for participants with a baseline CHD risk of 10% or greater ($p=0.017$). In this subgroup, the risk for risperidone-treated patients (−3.2, SE=0.6) remained lower than that for olanzapine (−0.9, SE=0.6), although not statistically significant with Bonferroni correction ($p=0.008$). For participants with less than 10% baseline CHD risk, change in risk did not differ across treatment groups.

Treatment comparisons for change in CHD risk were also examined by age and gender (Table 2). For those under 40 years of age, the change in CHD risk was significantly different across the antipsychotic groups ($p=0.016$) with olanzapine associated with increased risk compared to perphenazine ($p=0.004$) and ziprasidone ($p=0.004$) (Table 2). In participants ages 50 years and older, the change in CHD risk also significantly differed across the 5 antipsychotic groups ($p=0.008$), with olanzapine associated with significantly greater increase in risk compared to risperidone ($p=0.002$). The change in risk for quetiapine was also numerically higher than for risperidone ($p=0.009$), but not statistically significant with Bonferroni correction. The change in risk did not differ across the five treatment arms for the 40–49 age group. In addition, the overall change in 10-year estimated CHD risk differed significantly in male ($p=0.017$) but not in female subjects. In men, olanzapine was associated with numerically higher CHD risk compared to perphenazine ($p=0.007$) and risperidone ($p=0.008$), although not statistically

Table 3
Change in coronary heart disease risk factors in CATIE subjects from baseline to end of phase 1 by antipsychotic treatment group

	Overall	Olanzapine	Perphenazine	Quetiapine	Risperidone	Ziprasidone	*p*-value
Started smoking	52 (4)	11 (3)	9 (4)	13 (4)	14 (4)	5 (3)	NS
Quit smoking	48 (3)	11 (3)	8 (3)	13 (4)	10 (3)	6 (3)	
	1385	316	249	318	320	182	
New diabetes diagnosis	91 (6)	27 (8)	17 (7)	14 (4)	21 (6)	12 (6)	NS
	1460	336	261	337	341	185	
New hypertension diagnosis	152 (11)	35 (11)	23 (9)	37 (12)	32 (11)	25 (16)	NS
No longer hypertensive	141 (11)	21 (7)	30 (12)	32 (10)	37 (12)	21 (13)	
	1329	306	248	312	304	159	

Table entries are *n* (%), and sample size. Results based on the subset of the 1460 patients for whom these data were available for at least one follow-up visit.

significant with Bonferroni correction. Change in CHD risk at 3 months is also reported by age, gender, and baseline risk categories in Appendix Table 2, although treatment comparisons were not made due to very small samples sizes in these subgroups.

3.4. Changes in individual coronary heart disease risk factors

Analysis of individual cardiac risk factors revealed no difference between treatment groups for change in smoking status, new-onset diabetes or hypertension during phase 1 (Table 3). However, a trend for reduction in hypertension at 3 months was noted in the perphenazine group (Appendix Table 3). Changes in total and HDL cholesterol at end of phase significantly differed between groups ($p<0.001$ and $p=0.002$, respectively, adjusted comparisons) (Table 4). Total cholesterol was lowered more with risperidone (−11.2 mg/dl, SE=2.0) compared to olanzapine (0.8 mg/dl, SE=2.0, $p<0.001$) and quetiapine (−2.2 mg/dl, SE=2.0, $p=0.002$), whereas total cholesterol with ziprasidone (−9.3, SE=2.8) was lowered more than olanzapine only ($p=0.003$) (Fig. 3). A similar result was noted between risperidone and quetiapine in the 3-month fasting cohort (Appendix Table 4).

Across all patients, covariate-adjusted HDL cholesterol levels decreased in olanzapine (−1.4, mg/dl

Table 4
Changes in cholesterol in CATIE subjects from baseline to end of phase 1 by antipsychotic treatment group

	Olanzapine	Perphenazine	Quetiapine	Risperidone	Ziprasidone	*p*-value
Total cholesterol (mg/dl) (unadjusted)	−0.3±37.0[a]	−4.9±36.7	−1.5±37.8[b]	−10.0±37.6[a,b]	−8.9±36.0	0.010
	(286)	(219)	(271)	(271)	(143)	
Total cholesterol (mg/dl) (adjusted)[c]	0.8±2.0[d]	−3.8±2.3	−2.2±2.0[e]	−11.2±2.0[d,e]	−9.3±2.8[d]	<0.001
	(286)	(219)	(271)	(271)	(143)	
HDL cholesterol (mg/dl)						
Overall (unadjusted)	−1.0±9.4[f]	1.3±8.7[f]	−0.3±9.6	0.1±10.3	1.7±10.3[f]	0.026
	(286)	(219)	(271)	(271)	(144)	
Overall (adjusted)[g]	−1.4±0.5[h]	1.1±0.6[h]	−0.1±0.5	0.4±0.5	1.9±0.7[h]	0.002
	(286)	(219)	(271)	(271)	(142)	
Other races[i]	−0.9±0.9[j]	−1.3±1.0[j]	0.0±1.1	0.9±0.9	4.3±1.4[j]	0.012
	(115)	(88)	(85)	(109)	(51)	
Whites[i,k]	−1.7±0.6[l]	2.7±0.7[l,m]	−0.2±0.6[l]	0.0±0.6[m]	0.6±0.9	<0.001
	(171)	(131)	(186)	(162)	(91)	

Table entries are ANCOVA least squares adjusted Mean±SE, (n) except for unadjusted results with Mean±SD, (n). Results based on the subset of the 1460 patients for whom these data were available for at least one follow-up visit.

[a] Difference in total cholesterol change statistically significant with the Bonferroni correction for Olanzapine compared to Risperidone ($p=0.002$).

[b] Difference in total cholesterol change numerically different for Quetiapine compared to Risperidone ($p=0.008$), but not statistically significant with the Bonferroni correction.

[c] Model adjusted for total cholesterol at baseline and time to treatment discontinuation.

[d] Difference in total cholesterol change statistically significant with the Bonferroni correction for Olanzapine compared to Risperidone ($p<0.001$) and Ziprasidone ($p=0.003$).

[e] Difference in total cholesterol change statistically significant with the Bonferroni correction for Quetiapine compared to Risperidone ($p=0.002$).

[f] Difference in HDL change numerically different for Olanzapine compared to Perphenazine ($p=0.009$) and Ziprasidone ($p=0.007$), but not statistically significant with the Bonferroni correction.

[g] Adjusted for baseline HDL cholesterol, time to treatment discontinuation, age, gender, and race. In a separate model which considered a treatment by race interaction, this effect was found to be significant ($p=0.002$). Treatment comparisons are presented separately for whites and other races.

[h] Difference in HDL change statistically significant with the Bonferroni correction for Olanzapine compared to Perphenazine ($p=0.001$) and Ziprasidone ($p<0.001$).

[i] Adjusted for baseline HDL cholesterol, time to treatment discontinuation, age, and gender.

[j] Difference in HDL change statistically significant with the Bonferroni correction for Ziprasidone compared to Olanzapine ($p=0.002$) and Perphenazine ($p=0.001$).

[k] A significant Ziprasidone cohort effect was found for whites ($p=0.001$). Comparisons between Ziprasidone and other treatments among the whites should be limited to the results in the ziprasidone cohort ($N=438$). In this cohort, a numerical difference was found for HDL change in Perphenazine (4.0±1.0, $N=74$) compared to Ziprasidone (0.5±0.9, $N=91$), but it was not significant using the Bonferroni correction ($p=0.008$).

[l] Difference in HDL change statistically significant for Perphenazine compared to Olanzapine ($p<0.001$) and to Quetiapine ($p=0.002$) using the Bonferroni correction.

[m] Difference in HDL change numerically different for Perphenazine compared to Risperidone, but not statistically significant with the Bonferroni correction ($p=0.005$).

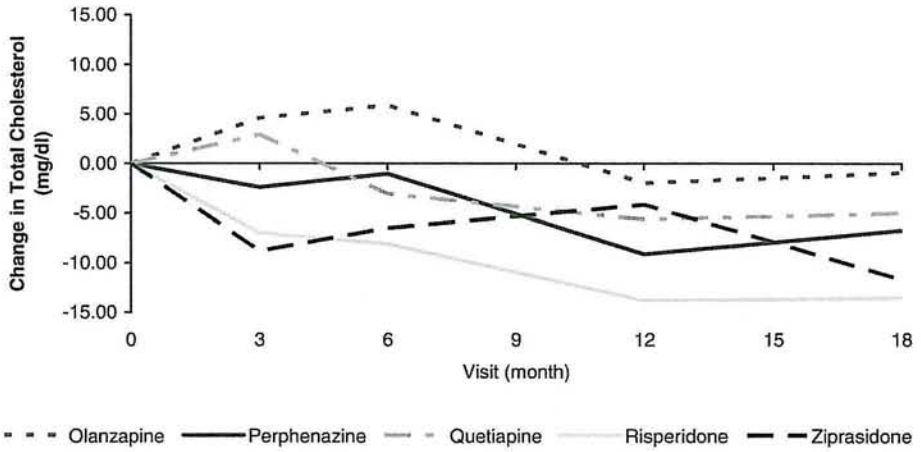

Fig. 2. Repeated measures estimates of total cholesterol changes. Olanzapine shown in red; perphenazine shown in blue; quetiapine shown in green; risperidone shown in yellow; ziprasidone shown in black dashed line. Between group differences significant for olanzapine vs. risperidone ($p<0.001$), olanzapine vs. ziprasidone ($p<0.001$) and quetiapine vs. risperidone ($p=0.001$). Change numerically different for olanzapine vs. perphenazine, but not statistically significant with Bonferroni correction ($p=0.009$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Sample sizes by visit and treatment group are

Visit	Olanzapine	Perphenazine	Quetiapine	Risperidone	Ziprasidone
3	269	208	257	261	140
6	200	130	163	175	74
12	157	85	109	126	55
18	129	66	64	97	37

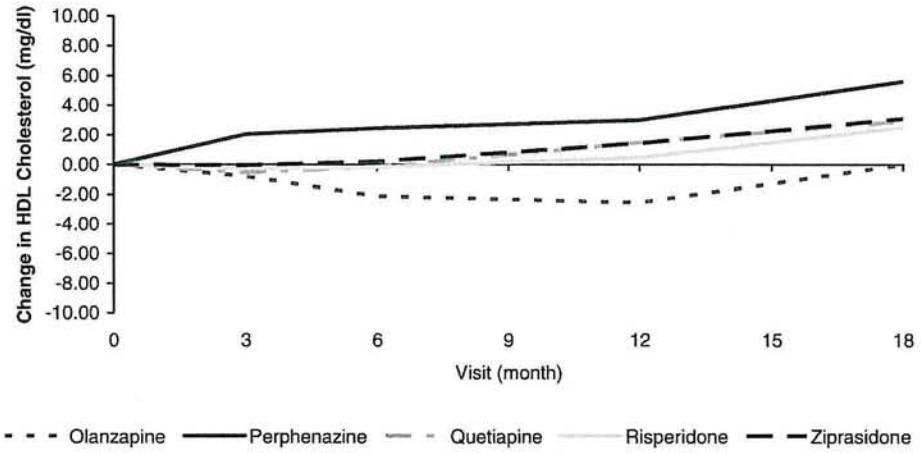

Fig. 3. Repeated measure estimates of HDL cholesterol changes for whites. Olanzapine shown in red; perphenazine shown in blue; quetiapine shown in green; risperidone shown in yellow; ziprasidone shown in black dashed line. Between group differences significant in whites for perphenazine vs. olanzapine ($p<0.001$), quetiapine ($p=0.002$), and risperidone ($p=0.003$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Sample sizes by visit and treatment group are

Visit	Olanzapine	Perphenazine	Quetiapine	Risperidone	Ziprasidone
3	161	122	179	157	89
6	117	82	108	108	43
12	96	49	72	79	35
18	79	41	45	63	24

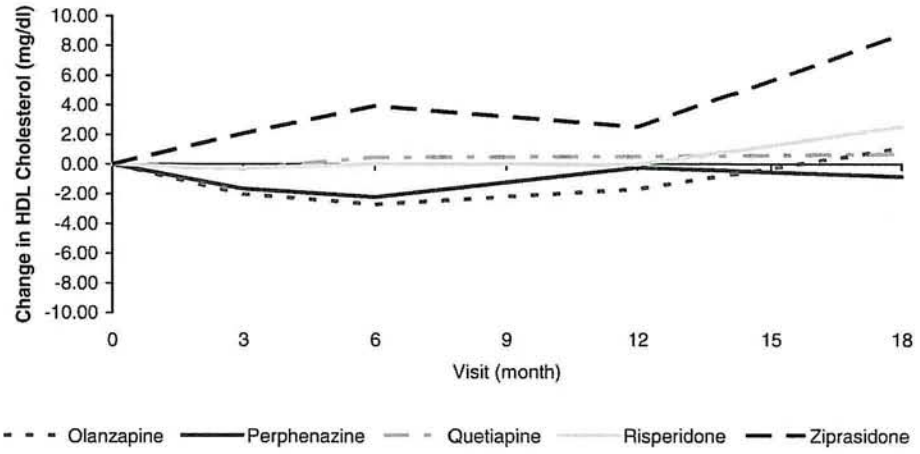

Fig. 4. Repeated measures estimates of HDL cholesterol changes for other races. Olanzapine shown in red; perphenazine shown in blue; quetiapine shown in green; risperidone shown in yellow; ziprasidone shown in black dashed line. Between group differences significant in other races for ziprasidone vs. olanzapine ($p<0.001$) and perphenazine ($p=0.002$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Sample sizes by visit and treatment group are

Visit	Olanzapine	Perphenazine	Quetiapine	Risperidone	Ziprasidone
3	108	86	78	104	49
6	83	48	55	67	30
12	61	36	37	47	20
18	50	25	19	34	13

SE=0.5) compared to an increase in perphenazine (1.1 mg/dl, SE=0.6, $p=0.001$) and ziprasidone (1.9 mg/dl, SE=0.7, $p<0.001$). However, an interaction between treatment and race was identified. For whites, HDL was significantly increased in the perphenazine treatment group (2.7 mg/dl, SE=0.7) compared to olanzapine (−1.7 mg/dl, SE=0.6; $p<0.001$) and quetiapine (−0.2 mg/dl, SE=0.6; $p=0.002$) (Fig. 3). For non-whites, ziprasidone-treated patients had an increase in HDL (4.3 mg/dl, SE=1.4) compared to a decrease for both olanzapine (−0.9 mg/dl, SE=0.9; $p=0.002$) and perphenazine (−1.3 mg/dl, SE=1.0; $p=0.001$.) (Fig. 4). There was no difference between treatment groups for change in HDL at 3 months (Appendix Table 4). Results of mixed model analyses for total and HDL cholesterol were consistent with findings from the end of phase ANCOVA analyses (Figs. 2–4).

4. Discussion

This prospective, randomized study provides an opportunity to study change in overall coronary heart disease risk across antipsychotic treatments for patients with schizophrenia in a large clinical trial. At baseline, study participants had high estimated 10-year CHD risk compared to matched controls from the general population and had been treated for schizophrenia for an average of 14 years (Goff et al., 2005). In the relatively short study time frame consisting of a maximum treatment exposure of 18 and mean of 9.5 (SD 7.0) months, overall differences in estimated 10-year CHD risk between antipsychotics were significant. Olanzapine and quetiapine were associated with increased risk; whereas risk decreased in patients treated with perphenazine, risperidone, and ziprasidone. The difference in 10-year CHD risk between olanzapine and risperidone was statistically significant ($p=0.004$). Differences between medication effects on risk were seen particularly in patients with at least 10% baseline CHD risk, in subjects younger than 40 and older than 49, and in men. Coronary heart disease risk increased, on average, for subjects with baseline risk estimated at less than 10%, whereas average estimated risk was reduced in subjects entering the study with estimated 10-year CHD risk of 10% or greater. Overall differences in CHD risk between treatments appeared to result largely from lowering of total cholesterol in subjects treated with risperidone and ziprasidone, and elevation of HDL cholesterol among whites treated with perphenazine and non-whites treated with ziprasidone.

While other work documents changes in individual CHD risk factors such as diabetes mellitus and cholesterol from particular antipsychotics (Allison et al., 1999; American Diabetes Association and American Psychiatric Association, 2004; Meyer and Koro, 2004; Newcomer and Haupt, 2006), this analysis is distinctive in examining overall CHD risk across several antipsychotics in the setting of a large, randomized clinical trial. Our results also are consistent with those from a recent post-hoc analysis using the Framingham equation to compare change in CHD risk in patients treated with olanzapine and ziprasidone in a 6-week randomized clinical trial (Del Valle et al., 2006).

Differences in individual antipsychotic drug effects on CHD risk in the CATIE study appear to be due principally to changes in total and HDL cholesterol. Whereas other agents tended to decrease total cholesterol, olanzapine was associated with relative increases. Prior reports have demonstrated large increases in triglyceride levels with olanzapine (Meyer, 2002; Wirshing et al., 2002; Atmaca et al., 2003), whereas risperidone and ziprasidone have been associated with small or neutral effects on triglycerides and total cholesterol (Kingsbury et al., 2001; Meyer, 2002; Atmaca et al., 2003; Weiden et al., 2003). While risperidone's effects on weight gain and glucose elevation are similar to quetiapine, (Lieberman et al., 2005) because risperidone was associated with decreases in total cholesterol in this study, its estimated CHD risk is comparable to that of ziprasidone and perphenazine.

Quetiapine, which also increased mean 10-year CHD risk in those ages 50 years and older, has been shown to increase trigylcerides, although most studies show a smaller impact on total cholesterol levels compared to olanzapine (Meyer, 2001; Shaw et al., 2001; Atmaca et al., 2003). Perphenazine decreased mean 10-year CHD risk compared to olanzapine in those under 40 years, those 50 years and older and men, although previous studies have shown that phenothiazines increase levels of trigylcerides and LDL (Serafetinides et al., 1972; Sasaki et al., 1985).

Consistent with our hypothesis, effects on HDL cholesterol differed significantly among antipsychotics, with only olanzapine associated with a consistent mean decrease (or worsening) in HDL levels. To our knowledge, the mediating effect of race observed on perphenazine-associated changes in HDL cholesterol has not been previously reported. Whites treated with perphenazine exhibited a mean increase in HDL cholesterol, whereas levels decreased in other races. If replicated, identification of physiologic or molecular mechanisms underlying race differences in antipsychotic effects on HDL will be of considerable interest.

The mechanisms for antipsychotic-related dyslipidemia are not fully understood. Certainly weight gain and glucose intolerance are well known to increase risk of hyperlipidemia, yet we also know that these factors are not necessary for antipsychotic-induced adverse changes in lipid profiles to occur (Meyer et al., 2005).

While we found significant differences in lipids across antipsychotic medications, we did not see changes in the dichotomous risk factors of diabetes between drugs over the study. In part, this may be due to our definition and the study's limited duration. A patient could only obtain a new diagnosis of diabetes but could not revert from diabetic to non-diabetic if blood sugars decreased. In addition, any changes in glucose not meeting the threshold for diabetes did not influence the calculation of CHD risk using the Framingham score. While the definition of diabetes used for this analysis differs from that used in the original Framingham Study (i.e., two casual blood glucoses of 150 mg/dl or fasting of >140), it reflects the investigators' best attempt to categorize risk factors according to currently accepted definitions using available study data.

We also did not see changes in hypertension status across antipsychotics. However, while the hypertension definition we used also was dichomotous and does not reflect smaller, potentially significant changes in blood pressure, hypertension in the Framingham score is more sensitive and incorporates changes in JNC-V blood pressure stages (e.g., change from systolic 140–159 mmHg to 160 mmHg) We found qualitative differences in changing blood pressure stage by antipsychotic, with approximately 36% of patients taking olanzapine, quetiapine or ziprasidone worsening their blood pressure stage, and 27% of patients taking perphenazine or risperidone worsening blood pressure stage. Fourteen percent of participants took anti-hypertensives at baseline, and 3% initiated anti-hypertensives during the study; these did not differ significantly by antipsychotic assignment. Meyer et al. provides a more detailed analysis of blood pressure and other components of the metabolic syndrome (Meyer et al., 2008). We also clarify that the blood pressure criteria for the baseline CHD risk CATIE sample used systolic of >140 mmHg and diastolic >90 mmHg (Goff et al., 2005). Blood pressure criteria for the metabolic syndrome are systolic>=135 and diastolic>=85 mmHg (McEvoy et al., 2005).

We found particular benefit in CHD risk reduction in those patients with greater than 10% CHD risk at baseline treated with perphenazine, risperidone and ziprasidone. Using these medications could have positive consequences in patients who already have clinical risk for coronary disease including possible

metabolic side effects from prior antipsychotics. While there was no difference across treatment groups in patients with less than 10% baseline CHD risk, it is notable that risk appeared to increase from baseline in almost all treatment groups.

To explore if switching or staying on an antipsychotic influenced CHD risk, we examined the subsample of patients (n=216) who were on either olanzapine or risperidone prior to randomization and were randomized to either of these two treatments. We found no statistically significant difference in CHD risk between remaining or switching to the other antipsychotic in this limited sample (results not shown).

In addition to results presented here, Appendix A includes results from the subpopulation of participants with fasting laboratory samples at baseline and 3 months in order to approximate our original baseline CHD risk analysis (Goff et al., 2005). Numerically, findings were similar overall, although the sample size for each treatment was very small.

This study has limitations. First, although the CATIE Schizophrenia Trial is unique in its large sample size and its examination of several antipsychotic therapies, CATIE was not designed to examine CHD risk as a primary outcome. We attempted to match the Framingham definitions of CHD risk factors, but definitions for hypertension, tobacco smoking and diabetes did differ somewhat. Second, while the Framingham formula is valid across many populations, the equation has not been validated in populations taking antipsychotics. The rapid and large weight change associated with some antipsychotics substantially differs from typical weight change patterns in the general population from which the risk equation was derived. Because weight is not a variable in the Framingham equation, it is possible that the long-term impact on cardiac health of rapid antipsychotic-induced weight gain may not be sufficiently captured. Moreover, although triglycerides are part of total cholesterol which is in the Framingham equation, the model does not specifically incorporate risk for triglycerides, which are increasing in acceptance as an independent risk factor for coronary disease (Nordestgaard et al., 2007) and often the lipid fraction most affected by antipsychotics. We would expect inclusion of weight and triglycerides in a CHD risk model would influence and likely enhance the differences we found between antipsychotics with the Framingham model.

In conclusion, we found that different antipsychotic treatments did indeed confer varying levels of CHD risk in the CATIE Schizophrenia Trial. Subjects were treated with psychotropics 14 years on average before joining the study, and much cardiovascular risk may have been expected to have accumulated prior to the trial; this is supported by the high baseline Framingham risk scores. Despite this high initial risk factor burden, CHD risk changes differed significantly in magnitude across antipsychotic agents after only a few months of exposure. The absolute magnitude of changes in CHD risk found with antipsychotic medications are comparable to those seen in an intensive lifestyle modification program for adults with cardiac risk factors and thus should be clinically important (Ellsworth et al., 2004). Olanzapine conferred the highest risk of the antipsychotics, with quetiapine appearing to have similar risk. Risperidone, ziprasidone and perphenazine were associated with lower overall risk. The largest treatment differences in 10-year CHD risk were seen in participants with at least 10% baseline CHD risk and in older subjects. When initiating or changing antipsychotic therapy, clinicians should consider these changes in likelihood of coronary heart disease, particularly for older patients and those with baseline coronary risk factors.

Role of funding source

The CATIE Schizophrenia Trial was supported by National Institute of Mental Health, Grant No. 1MH900001. The NIMH and study principal investigators are responsible for the design and conduct of the trial, and the primary analyses. There is no industry involvement in these activities.

Contributors

Drs. Lieberman and Stroup led the CATIE Schizophrenia Study, Dr. Hsiao worked with them to design the protocol; Drs. McEvoy, Goff, Meyer, Nasrallah and Daumit comprised the working group for this manuscript. Drs. Davis and Davis performed statistical analyses.

Conflict of interest

Dr. Rosenheck reports having received research funding from AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb, and Eli Lilly and Co.; and consulting fees from Bristol-Myers Squibb, Eli Lilly and Co., and Janssen Pharmaceutica Products. Dr. Lieberman reports having served as a consultant and/or advisor for Acadia, Astra Zeneca, Eli Lilly, GlaxoSmithKline, Lundbeck, Organon, and Pfizer He does not receive financial compensation or salary support for his participation as a consultant or as a member of an advisory board. He has received grant support from Acadia, Bristol-Myers Squibb, GlaxoSmithKline, Janssen Pharmaceutica, Merck, Organon, and Pfizer. He holds a patent from Repligen. Dr. McEvoy reports having received research funding from AstraZeneca, Forest Research Institute, Eli Lilly and Co., Janssen Pharmaceutica, and Pfizer Inc.; consulting or advisory board fees from Pfizer Inc. and Bristol-Myers Squibb; and lecture fees from Janssen Pharmaceutica, and Bristol-Myers Squibb. Dr. Meyer reports having received research support from Bristol-Myers Squibb and Pfizer, Inc., and has received speaking or advising fees from Bristol-Myers Squibb, Janssen Pharmaceutica, Pfizer, Inc., and Wyeth. Dr. Sonia Davis reports that she is an employee of Quintiles, Inc. Dr. Stroup reports he has consulted or received payment for speaking at events for AstraZeneca, Janssen, Lilly, Pfizer and Solvay. Dr. Nasrallah has received grants/

research support from AstraZeneca, GSK, Jannsen, Lilly, Pfizer and Sanofi; has been a consultant, an advisory board member and served on the speakers' bureau for Abbott, AstraZeneca, Janssen, Pfizer and Shire. Dr. Goff has received grants/research support from Pfizer, Cephalon and Janssen, has received consulting, advisory board or lecture fees from Dainippon Sumitomo, Solvay/Wyeth, BristolMyerSquibb, Organon, Vanda and Eli Lilly. Dr. Daumit, Dr. Davis and Dr. Hsiao have no competing interests.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.schres.2008.07.006.

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