Predicted Risk of Diabetes and Coronary Heart Disease in Patients With Schizophrenia: Aripiprazole Versus Standard of Care

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Objective: Patients with schizophrenia are at increased risk of developing diabetes mellitus and cardiovascular disease. Furthermore, some atypical antipsychotics are associated with metabolic disturbances, which augment the risk for these comorbid conditions. In clinical trials, effects on metabolic parameters with aripiprazole are similar to those with placebo and superior to those with olanzapine, and the Schizophrenia Trial of Aripiprazole (STAR) demonstrated comparable efficacy of aripiprazole versus standard of care (SoC; physicians' selection of quetiapine, olanzapine, or risperidone).

Method: In this post hoc analysis, data from STAR were used to assess the risks of diabetes and coronary heart disease (CHD) in patients with schizophrenia. The Stern (San Antonio Heart Disease Study) and Framingham models, with modifications, were used to predict the risk of diabetes at 7.5 years and CHD at 10 years, respectively.

Results: Aripiprazole-treated patients had more favorable changes in lipids, glucose, and body weight versus SoC. In a subsample of patients who had fasting lipid and glucose test results, the Stern model predicted 23.4 fewer incidences of new-onset diabetes with aripiprazole versus SoC in a hypothetical 1000-patient cohort. The number needed to treat with aripiprazole to avoid 1 adverse outcome expected with SoC was 43. In the same population, the Framingham model predicted 3.9 fewer CHD events, with a number needed to treat with aripiprazole of 256.

Conclusion: Aripiprazole-treated patients had more favorable changes in metabolic parameters compared with SoC, leading to a reduced risk of diabetes and CHD, based on validated models.

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There is now considerable evidence to show that patients with schizophrenia are at an increased risk for developing diabetes mellitus and cardiovascular disease. For example, in a British cohort of patients treated for schizophrenia who were living outside the hospital, mortality linked to diabetes showed a 10-fold increase over the average for the general population, whereas mortality linked to cardiovascular disease was almost double the expected rate.[1] Similarly, elevated rates of cardiovascular mortality have also been observed in schizophrenia patients in Sweden.[2,3] Data from a U.S. study in a large managed care organization showed that, compared with the general population, the risk of myocardial infarction was increased nearly 5-fold in patients with schizophrenia receiving antipsychotic therapy. In addition, the risk of new-onset diabetes was increased by 75% in antipsychotic-treated patients.[4] However, existing research does not quantify the effect of treatment on risks for these diseases.

Previous studies have also demonstrated that patients with schizophrenia have a high prevalence of risk factors

for both coronary heart disease (CHD) and diabetes.[5–7] Using the Framingham CHD function, analysis comparing baseline data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and data from subjects in a community sample provides evidence for a higher risk of CHD in patients with schizophrenia, as derived from higher levels of smoking, diabetes, and hypertension and lower levels of high-density lipoprotein (HDL) cholesterol.[5] Overall, the 10-year risk of CHD was significantly increased in men (9.4% vs. 7.0%) and women (6.3% vs. 4.2%) with schizophrenia compared with age-, race-, and gender-matched controls ($p = .0001$). In addition, lifestyle factors may play a role in elevating diabetes and CHD rates, including high-fat, low-fiber diets; obesity; lack of exercise; and high rates of smoking.[8]

Atypical antipsychotic agents are widely prescribed for patients with schizophrenia and achieve beneficial effects on negative, cognitive, and affective symptoms. Although atypical antipsychotics have reduced concerns over the neurologic side effects seen with typical antipsychotics, accumulating evidence shows that some of these agents are associated with potentially troublesome metabolic consequences, including clinically significant weight gain, dyslipidemia, and glucose dysregulation.[9,10] In turn, these metabolic changes, which are associated more strongly with some individual atypical antipsychotic agents, may increase the risk of CHD in this already vulnerable patient population.[11–14]

In general, similar efficacy among atypical antipsychotics has been shown, as exemplified by CATIE—a multicenter, randomized study that compared antipsychotic agents (olanzapine, quetiapine, risperidone, ziprasidone, and perphenazine) in a sample of 1493 patients with schizophrenia during 18 months of treatment.[12] In CATIE, olanzapine was the most effective in terms of overall discontinuation rate, with few differences between the other antipsychotics. There was, however, considerable variability in antipsychotic-related metabolic changes between different second-generation agents. For example, the percentage of patients who gained at least 7% of their baseline body weight was greater with olanzapine than with other treatments (30% vs. 7%–16%, $p < .001$),[12] and these results are consistent with those of other studies of antipsychotic-related metabolic changes.[15–17]

Aripiprazole was not included in CATIE, as it had not been licensed in the United States at the time the study was initiated. Aripiprazole has a similar metabolic profile to placebo in studies with patients with schizophrenia,[18] and, compared with olanzapine, aripiprazole has favorable effects on body weight and lipids.[19] A comparison of aripiprazole with other second-generation antipsychotics was provided by the Schizophrenia Trial of Aripiprazole (STAR; Study CN138-152)—a randomized, open-label study conducted in 12 European countries (France, Sweden, Hungary, Spain, United Kingdom, Germany, Denmark, Czech Republic, Finland, Austria, The Netherlands, and Norway). In this study, aripiprazole was compared with standard of care (SoC), whereby SoC consisted of physicians' selection of quetiapine, olanzapine, or risperidone.[20] Quetiapine, olanzapine, and risperidone were selected as SoC treatments, as these were the atypical antipsychotic agents available for the treatment of schizophrenia in Europe at the time of the study. Results from STAR showed that aripiprazole was superior to SoC on the Investigator Assessment Questionnaire.[21] In the 2 treatment groups, mean Clinical Global Impressions-Improvement scores and mean changes in Clinical Global Impressions-Severity of Illness scores were similar.[22]

Under the STAR protocol, metabolic data were collected as part of prespecified secondary safety outcomes. The post hoc analysis presented here uses baseline and end-of-study results from STAR and validated predictive models to assess the long-term risk of diabetes and CHD in patients with schizophrenia receiving aripiprazole or SoC agents. Although a previous study[5] modeled CHD risks in a population of patients with schizophrenia, this is the first study to examine differential risks linked to antipsychotic treatment.

METHOD

Study Design

The probabilities of diabetes and CHD were modeled using published algorithms and patient data from the randomized, open-label STAR study.[20] Computations of baseline and end-of-study disease risks used patient-level data stratified by treatment; the change from baseline in estimated disease risk was calculated within treatment groups (aripiprazole vs. SoC). The absolute risk difference (ARD) was used to project results for a hypothetical population of 1000 patients, and the number needed to treat (NNT) was ascertained to identify the number of patients who would need to be treated with the preferred drug to avoid 1 incidence of disease. To evaluate the generalizability of results from U.S. and European populations, baseline data from STAR were compared with those from CATIE using reported summary data. Normal distribution of equal variance was assumed for continuous variables, and the Pearson χ^2 test was applied for categorical variables.

Data Source

Patient data used in the disease models were taken from STAR. Between July 2004 and June 2005, 555 patients were randomly assigned (1:1) to 26 weeks of treatment with aripiprazole (15–30 mg/day; N = 284) or SoC (N = 271). Completion rates with aripiprazole and SoC were 58% and 61%, respectively. Metabolic data col-

lected included fasting glucose, fasting total cholesterol, fasting HDL cholesterol, fasting low-density lipoprotein (LDL) cholesterol, and fasting triglycerides, as well as changes in body weight. While the protocol specified that fasting blood should be drawn, blood could be drawn from nonfasting patients providing the fasting state was documented. A central laboratory was used for all laboratory tests. Full details of the STAR study have been published previously.[20]

Prediction of Diabetes

The Stern model from the San Antonio Heart Disease Study (SAHDS) was used to predict the risk of diabetes at 7.5 years.[22] Variables included in the Stern model were age, gender, ethnicity, fasting glucose level, systolic blood pressure, HDL cholesterol level, body mass index (BMI), and parental or sibling history of diabetes. A number of adaptations to the Stern model were carried out for use in the present analysis. As more than 96% of patients in STAR were identified as white, all patients were classified as white to fit the classification in the original SAHDS sample as non-Hispanic white or Mexican American. As data on parental or sibling history of diabetes were not available, the present study applied the rate of diabetes in parents and siblings among non-Hispanic white persons from the SAHDS sample (21.0% in male patients and 15.6% in female patients).[22] Fasting status for glucose and cholesterol levels was not uniformly achieved in STAR. Therefore, a subsample with fasting values was identified and comparability between groups was evaluated. Disease modeling was performed twice: with fasting subjects only and with all subjects.

Prediction of CHD

The Framingham model was used to predict risk of CHD within 10 years.[23] The variables used in the Framingham study were age, fasting HDL and LDL cholesterol levels, blood pressure, diabetes status, and current smoking. In the Framingham study, determination of diabetes included treatment with insulin or oral agents, 2 random blood glucose levels > 150 mg/dL, or 1 fasting blood glucose level > 140 mg/dL. In the current study, a positive diabetes status was based on treatment with insulin or oral agents or fasting blood glucose level ≥ 126 mg/dL to reflect the most recent guidelines of the American Diabetes Association.[24] Other modifications were applied: (1) in the original Framingham model, an average of 2 seated blood pressure measurements was used, compared with a single measurement in the present study; (2) only fasting lipid values were used in the original model—here, disease modeling was performed twice, with fasting subjects only and with all subjects; and (3) a substitution for actual smoking was based on current smoking rates in a Scottish sample of patients with schizophrenia of 71% in males and 42% in females.[25]

Statistical Analysis

Analyses were conducted for all subjects in the STAR safety sample (all subjects who received at least 1 dose of study medication) (N = 548), as well as the subsample who had fasting laboratory values. In the fasting subsample, continuous and categorical baseline characteristics were analyzed with t tests and χ^2 or Fisher exact tests, respectively.

Change from baseline to week 26 in lipid measures, glucose, and weight used analysis of covariance and controlled for baseline values and other relevant dimensions. Last-observation-carried-forward (LOCF) methodology was used for subjects who discontinued prior to the end of the study.

As previously described, published algorithms were used to model the risk of diabetes and CHD, based on risk levels at baseline and at the conclusion of STAR. Moreover, reporting of disease risk focuses on results in the subsample with fasting values, although risk calculations for the total sample (fasting and nonfasting) are included in the tables. For each disease model, 1 required parameter was not assessed in the STAR study, and the proportion from a relevant published study was substituted. Accordingly, for smoking status in Framingham, gender-stratified proportions from a European study of patients with schizophrenia were applied to both treatment arms.[25] Patients with missing baseline and/or endpoint risk factors were excluded, and, in the modeling of diabetes risk, patients with preexisting diabetes were excluded. LOCF was used as the imputation method. To calculate the estimated change of risk, the estimated disease risk at week 26 was subtracted from the estimated risk at baseline. The difference in the estimated change of risk in 26 weeks between the 2 arms was attributed to the difference in treatment.

If treating with aripiprazole compared to SoC, the NNT is the number of patients that are needed to treat in order for 1 diabetes/CHD case to be avoided. The NNT (NNT = 1/ARD) was calculated,[26] and the results were projected to a hypothetical population of 1000 patients.

RESULTS

Baseline and Follow-Up Characteristics of STAR Study Sample

Baseline characteristics are shown in Table 1, presented for all patients in the safety sample (N = 548) and for the subsample of patients who had results of fasting lipids/glucose tests (N = 262). Baseline risk parameters were similar across aripiprazole and SoC arms for patients in the fasting state.

As shown in Table 2, STAR results indicated that patients treated with aripiprazole had more favorable changes in lipids and weight versus those treated with SoC. In general, these differences were statistically

Table 1. Sample Description at Baseline: Total Safety Sample and Fasting Subsample

	Total Sample										Fasting Subsample			
	Aripiprazole		Standard of Care		Olanzapine[a]		Quetiapine[a]		Risperidone[a]		Aripiprazole[b]		Standard of Care[b]	
Parameter	N	Value[c]	N	Value[c]	N	Value[c]	N	Value[c]	N	Value[c]	N	Value[c]	N	Value[c]
Gender, % male	282	59.6	266	60.2	75	62.7	110	58.2	81	60.5	133	57.9	129	56.6
Age, y	282	38.1 (10.9)	266	38.9 (11.1)	75	39.9 (11.2)	110	38.5 (10.8)	81	38.7 (11.6)	133	37.3 (10.9)	129	37.7 (10.3)
Body mass index	280	27.2 (5.2)	263	27.3 (5.1)	75	27.0 (4.6)	108	27.9 (5.6)	80	26.8 (4.9)	132	26.6 (4.8)	128	27.0 (5.0)
Systolic blood pressure, mm Hg	277	124.0 (15.7)	260	124.0 (14.4)	74	125.7 (13.7)	106	123.5 (15.4)	80	123.0 (13.5)	130	123.8 (15.9)	126	122.4 (13.4)
Total cholesterol, mg/dL	282	210.8 (44.6)	266	211.7 (40.6)	75	208.7 (42.6)	110	212.1 (39.5)	81	214.1 (40.4)	133	212.9 (45.0)	129	207.1 (37.1)
HDL cholesterol, mg/dL	282	49.7 (13.6)	266	50.9 (15.1)	75	50.8 (15.7)	110	51.9 (15.5)	81	49.7 (13.9)	133	49.7 (13.4)	129	50.4 (15.3)
LDL cholesterol, mg/dL	281	123.2 (39.5)	263	123.9 (32.5)	75	124.6 (32.9)	110	121.6 (33.5)	78	126.6 (30.9)	133	124.2 (39.3)	128	123.4 (32.1)
Triglycerides, mg/dL	281	193.5 (138.3)	262	189.5 (137.1)	75	170.9 (111.4)	109	197.9 (146.0)	78	195.7 (146.3)	133	200.0 (161.7)	127	170.1 (109.0)
Glucose level, mg/dL	238	99.2 (20.8)	227	98.6 (19.6)	67	99.2 (18.8)	92	101.0 (23.9)	68	94.6 (12.0)	114	97.7 (22.0)	115	97.2 (15.94)

[a]Comparison between individual standard of care arms (olanzapine, quetiapine, and risperidone): p > .05 for all parameters.
[b]Comparison between subsample arms: p > .05 for all parameters.
[c]Shown as mean (SD) unless otherwise noted.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

Table 2. Differences in Risk Factor Levels in Total and Fasting Samples by Treatment: Change From Baseline to Week 26 (LOCF)

								Individual Standard of Care Treatments[b]					
	Aripiprazole		Standard of Care		Aripiprazole vs Standard of Care[a]			Olanzapine		Quetiapine		Risperidone	
Parameter	N	LS Mean (SE)	N	LS Mean (SE)	Difference	95% CI	p Value	N	LS Mean (SE)	N	LS Mean (SE)	N	LS Mean (SE)	p Value[c]
Total sample														
Total cholesterol, mg/dL	262	–20.3 (1.9)	245	–7.7 (1.9)	–12.6	–17.3 to –7.7	< .001	70	1.5 (3.1)	101	–10.3 (2.6)	74	–17.2 (3.0)	< .001
HDL cholesterol, mg/dL	262	2.0 (0.6)	245	0.4 (0.6)	1.6	0.2 to 3.0	.028	70	–0.8 (1.0)	101	0.6 (0.8)	74	–0.1 (0.9)	.520
LDL cholesterol, mg/dL	261	–13.3 (1.7)	242	–5.8 (1.8)	–7.5	–11.8 to –3.2	< .001	70	–0.3 (2.9)	101	–6.7 (2.4)	71	–13.3 (2.9)	.008
Triglycerides, mg/dL	261	–46.3 (5.9)	241	–13.0 (6.1)	–33.3	–48.3 to –18.4	< .001	70	10.4 (10.5)	100	–21.8 (8.8)	71	–17.0 (10.4)	.052
Weight, kg	279	–1.3 (0.3)	258	1.4 (0.4)	–2.7	–3.5 to –1.9	< .001	73	3.0 (0.5)	108	–0.2 (0.5)	77	0.4 (0.5)	< .001
Serum glucose, mg/dL	222	0.2 (1.6)	206	3.3 (1.7)	–3.1	–7.2 to 1.1	.146	60	5.9 (2.8)	84	2.5 (2.3)	63	3.2 (2.7)	.629
Fasting sample														
Total cholesterol, mg/dL	133	–18.8 (2.3)	129	–9.1 (2.3)	–9.7	–16.0 to –3.3	.003	37	4.1 (4.0)	51	–10.1 (3.4)	41	–17.3 (3.8)	< .001
HDL cholesterol, mg/dL	133	1.4 (0.6)	129	–0.6 (0.6)	2.0	0.3 to 3.6	.019	37	–2.1 (1.2)	51	0.6 (1.0)	41	–0.8 (1.1)	.213
LDL cholesterol, mg/dL	133	–11.6 (2.1)	128	–6.5 (2.2)	–5.1	–11.0 to 0.9	.093	37	–0.8 (3.9)	51	–6.4 (3.3)	40	–11.4 (3.7)	.152
Triglycerides, mg/dL	133	–41.2 (7.8)	127	–13.2 (7.9)	–28.0	–49.9 to –6.1	.012	37	34.9 (12.2)	50	–23.3 (10.5)	40	–25.4 (11.7)	< .001
Serum glucose, mg/dL	114	1.4 (1.4)	115	3.3 (1.4)	–1.9	–5.8 to 2.0	.335	31	3.2 (2.6)	47	3.0 (2.1)	37	3.7 (2.4)	.976

[a]Analysis of covariance (ANCOVA) controlling for baseline status, treatment, and fasting status (the latter dimension controlled only in total sample) for all laboratory values. Weight change analyzed using ANCOVA controlling for baseline status, treatment, and prior antipsychotic agent.
[b]Analysis of variance controlling for baseline status treatment and fasting status (except for weight and fasting samples).
[c]Overall difference among standard of care treatments.
Abbreviations: CI = confidence interval, HDL = high-density lipoprotein, LDL = low-density lipoprotein, LOCF = last observation carried forward, LS = least squares.

significant in both total and fasting samples, with the exception of LDL cholesterol in the fasting subsample (p = .093). The direction of change in glucose levels was more favorable with aripiprazole treatment, but this difference did not reach statistical significance. Comparison of the individual SoC treatments showed some differences between treatment groups.

Risk of Diabetes

Diabetes risk values calculated using the Stern model are shown in Table 3. For the subsample of fasting patients, the difference in change from baseline between the aripiprazole and SoC groups was –0.0234. Accordingly, in a hypothetical cohort of 1000 patients, the Stern model predicts 23.4 fewer incidences of new-onset diabetes over 7.5 years in patients receiving aripiprazole than in those receiving SoC. The NNT was 43.

Comparison of the individual SoC treatments shows that olanzapine, quetiapine, and risperidone all have an increase in diabetes risk (safety sample range, 0.034–0.039; fasting sample range, 0.018–0.025) compared to a decrease in risk with aripiprazole.

Risk of Coronary Heart Disease

CHD risk values calculated using the Framingham model are shown in Table 4. In the fasting subsample, the difference in change from baseline between aripiprazole and SoC was –0.0039, indicating that in a hypothetical cohort of 1000 patients, the Framingham model predicts 3.9 fewer CHD events over 10 years in patients receiving aripiprazole than in those receiving SoC. The NNT was 256.

Comparison of the individual SoC treatments shows that olanzapine and quetiapine both had a similar increase in CHD risk compared to a decrease in risk with aripiprazole and risperidone.

Comparison of European and U.S. Baseline Data

A comparison of baseline data from STAR and CATIE is presented in Table 5. All baseline data, with the exception of systolic blood pressure and glucose levels (fasting sample), were statistically significantly different between the studies. Over-

Table 3. Diabetes Risk Values Based on the Stern Model[a]

	Safety Sample Values[b]					Fasting Subsample Values Only				
			Standard of Care by Treatment					Standard of Care by Treatment		
Timing of Assessment	Aripiprazole (N = 211)	Standard of Care (N = 199)	Olanzapine (N = 58)	Quetiapine (N = 79)	Risperidone (N = 62)	Aripiprazole (N = 108)	Standard of Care (N = 111)	Olanzapine (N = 30)	Quetiapine (N = 45)	Risperidone (N = 36)
Baseline	0.1749 (0.2165)	0.1654 (0.2167)	0.1832 (0.2244)	0.1749 (0.2294)	0.1367 (0.1918)	0.1515 (0.1800)	0.1513 (0.1938)	0.1595 (0.2170)	0.1432 (0.1836)	0.1547 (0.1909)
Postbaseline	0.1649 (0.2206)	0.2027 (0.2611)	0.2171 (0.2665)	0.2142 (0.2698)	0.1746 (0.2464)	0.1507 (0.1975)	0.1739 (0.2244)	0.1835 (0.2257)	0.1685 (0.2269)	0.1728 (0.2262)
Change from baseline[c,d]	–0.0100 (0.2258)	0.0373	0.0340 (0.1836)	0.0394 (0.2557)	0.0379 (0.2032)	–0.0008 (0.1327)	0.0226	0.0240 (0.0862)	0.0252 (0.1684)	0.0181 (0.1678)

[a]Values expressed as mean (SD).
[b]Excludes patients with diabetes at baseline (aripiprazole, N = 10; standard of care, N = 7) or missing data on any diabetes risk component (aripiprazole, N = 61; standard of care, N = 60).
[c]Postbaseline disease risk was subtracted from risk at baseline.
[d]In the total study sample (fasting and nonfasting), the absolute risk difference and number needed to treat were –0.0473 and 21, respectively.

Table 4. Coronary Heart Disease Risk Values Based on the Framingham Model[a]

	Safety Sample Values[b]					Fasting Subsample Values Only				
			Standard of Care by Treatment					Standard of Care by Treatment		
Timing of Assessment	Aripiprazole (N = 256)	Standard of Care (N = 237)	Olanzapine (N = 70)	Quetiapine (N = 97)	Risperidone (N = 70)	Aripiprazole (N = 130)	Standard of Care (N = 125)	Olanzapine (N = 37)	Quetiapine (N = 49)	Risperidone (N = 39)
Baseline	0.0601 (0.0641)	0.0629 (0.0697)	0.0658 (0.0607)	0.0614 (0.0826)	0.0621 (0.0586)	0.0606 (0.0674)	0.0548 (0.0624)	0.0607 (0.0530)	0.0432 (0.0711)	0.0638 (0.0581)
Postbaseline	0.0565 (0.0626)	0.0630 (0.0686)	0.0700 (0.0684)	0.0619 (0.0728)	0.0576 (0.0629)	0.0547 (0.0582)	0.0529 (0.0573)	0.0649 (0.0557)	0.0452 (0.0637)	0.0510 (0.0494)
Change from baseline[c,d]	–0.0036 (0.0346)	0.0001	0.0043 (0.0320)	0.0005 (0.0317)	–0.0046 (0.0421)	–0.0058 (0.0373)	–0.0019	0.0042 (0.0343)	0.0020 (0.0262)	–0.0128 (0.0263)

[a]Values expressed as mean (SD).
[b]Excludes patients with missing data on any cardiovascular disease risk component (aripiprazole, N = 26; standard of care, N = 29).
[c]Postbaseline disease risk was subtracted from risk at baseline.
[d]In the total study sample (fasting and nonfasting), the absolute risk difference and number needed to treat were –0.0037 and 270, respectively.

Table 5. Baseline Profiles of CATIE and STAR Study Samples

Parameter	Total CATIE Sample[a] (A) N	Total CATIE Sample[a] (A) Value[d]	Fasting CATIE Sample[a] (B) N	Fasting CATIE Sample[a] (B) Value[d]	Total STAR Sample[b] (C) N	Total STAR Sample[b] (C) Value[d]	Fasting STAR Sample[b] (D) N	Fasting STAR Sample[b] (D) Value[d]	p Value[c] A vs C	p Value[c] B vs D
Gender, % male	1460	73.9	689	73.9	548	59.9	262	57.3	< .001	< .001
Race, % white	1458	60.0	687	63.5	548	96.5	262	97.7	< .001	< .001
Age, y	1460	40.6 (11.1)	689	40.4 (11.2)	548	38.5 (11.0)	262	37.5 (10.6)	< .001	< .001
Body mass index	1444	29.8 (7.0)	689	29.7 (7.0)	543	27.2 (5.1)	260	26.8 (4.9)	< .001	< .001
Systolic blood pressure, mm Hg	1457	124.6 (16.2)	689	123.9 (16.3)	537	124.0 (15.0)	256	123.1 (14.7)	.4545	.5053
HDL cholesterol, mg/dL	1447	43.5 (13.5)	689	43.7 (14.1)	507	50.4 (14.4)	262	50.0 (14.3)	< .001	< .001
Glucose level, mg/dL	…	…	688	98.6 (42.1)	428	98.9 (20.3)	229	97.5 (19.2)	…	.7023

[a]Data from McEvoy et al.[7] and Lieberman et al.[12]
[b]Values for total safety sample and fasting patients only.
[c]Differences were tested based on the reported summary data. Normal distribution of equal variance was assumed for continuous variables, and the Pearson χ^2 test was applied for categorical variables.
[d]Shown as mean (SD) unless otherwise noted.
Abbreviations: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness, HDL = high-density lipoprotein, STAR = Schizophrenia Trial for Aripiprazole.
Symbol: … = value not available.

all, patient characteristics appear more unfavorable in the CATIE (U.S.) cohort compared with the STAR (Europe) cohort, especially regarding BMI and HDL cholesterol.

DISCUSSION

Projected results from this analysis show that, in a hypothetical panel of 1000 patients, aripiprazole treatment is predicted to result in 23.4 fewer cases of new-onset diabetes compared with SoC. The calculated NNT of 43 indicates that aripiprazole treatment is predicted to prevent a new incidence of diabetes in 1 of every 43 patients treated. Projected results also show that in the hypothetical panel of 1000 patients, aripiprazole treatment is predicted to result in 3.9 fewer cases of CHD compared with SoC treatment, with 1 new case being prevented for every 256 patients treated. Thus, these results suggest that there could be long-term variation in diabetes and CHD incidence associated with the different metabolic profiles of the second-generation antipsychotics observed in previous studies.[11,12,14,27]

The difference between the NNTs for diabetes and CHD is notable and may reflect a conservative bias in using the Framingham model to predict the long-term risk of CHD. The Stern risk equation predicts a higher incidence of diabetes among patients treated with SoC relative to aripiprazole. Although the Framingham model includes diabetes status as a risk factor, the use of diabetes prevalence (at the conclusion of the study) in calculating postbaseline risk would not fully capture the predicted excess incidence of diabetes in the SoC arm during the observation period. Consequently, the present method is likely to minimize CHD risk.

Although no conclusions can be drawn from results of the individual SoC treatment arms due to small sample size, the similar direction of change in the individual treatment arms to the SoC population for diabetes and CHD risk shows that the differences between groups are not driven by one particular agent and supports the grouping of all 3 drugs into 1 SoC arm. However, we cannot rule out confounding by selection bias.

Consistent with guidelines for metabolic monitoring published in Europe[28,29] and the United States,[9] the choice of antipsychotic treatment should take into account drug-induced adverse metabolic changes and potential long-term consequences for individual health. Second-generation agents with a low propensity for weight gain and glucose intolerance should be considered for patients with, or at increased risk for, diabetes. In addition to the favorable metabolic profile of aripiprazole,[10] evidence suggests that treatment-emergent glucose abnormalities can be reversed following a switch to aripiprazole when detected early,[30] although similar results were not seen in patients switching due to weight gain.[31] Given the increased risk of diabetes and CHD in patients with schizophrenia, other strategies to reduce risk should also be considered in this population. In line with current recommendations these should include lifestyle advice, diet and exercise, weight loss, and, where appropriate, treatment for hypertension and abnormal cholesterol levels and smoking cessation.

Furthermore, because both diabetes and CHD increase health costs, the results of the present analysis also have potential economic implications. For example, on average, people with diabetes incurred US $13,243 in health care expenditures in 2002 compared with US $2560 for people without diabetes. When adjusting for differences in age, sex, and race/ethnicity, medical expenditures for people with diabetes were ~2.4 times higher than expenditures that would be incurred by the same group in the absence of diabetes.[32] For simple and complex myocardial infarction, a common type of CHD, average disease-related costs have been estimated at US $12,132 and US $15,198, respectively.[8]

The comparison of data from CATIE and STAR indicates that this analysis may underestimate risk if applied to a U.S. population, whereas U.S. data may overestimate the risk in European populations. In the U.S. sample enrolled in CATIE, the baseline risk of CHD and diabetes is likely to be higher, as a result of increased BMI, combined with a lower HDL cholesterol level.

Modeling has limitations relating to the use of certain assumptions and data-handling issues. For example, changes in risk levels were based on assessments conducted during a trial of 6 months' duration using LOCF data. Based on 1 year of follow-up in a study that compared olanzapine with aripiprazole treatment, use of shorter-term data would underestimate the differences in LDL and HDL cholesterol risk levels linked to the 2 treatments, although much of the change observed at 52 weeks is present at week 28.[33] As this study addressed changes in metabolic risk over 6 months, the longer-term effect of treatment on metabolic risk remains to be established. Metabolic levels were assumed to be constant for the duration of the modeling period (i.e., 7.5 or 10 years) and may, therefore, underestimate or overestimate risk for patients whose circumstances change, such as a switch of antipsychotic or initiation of statin or blood-pressure therapy. Use of LOCF data results in an "endpoint" estimate of risk that reflects the risk at the time of dropout for those patients who discontinued the study early and for those who completed the trial. A further limitation is that the model did not account for prior antipsychotic exposure. However, while metabolic changes after antipsychotic switch may be affected by prior antipsychotic medication, prior medication use in the aripiprazole and SoC arms was similar and is unlikely to have impacted on the findings of this analysis.

The Framingham model has been validated in U.S. and European populations,[34,35] although recent evaluations suggest that it may overestimate CHD incidence in Europe.[36–38] In contrast, utilization of the Stern model is more limited. Although developed and validated in a U.S. general community sample, subsequent evaluation in a German population-based study showed that its sensitivity and specificity were similar to those of the glucose tolerance test (the current "gold standard" for diagnosis of diabetes).[39]

To date, there has been no validation of the Stern and Framingham models in patients with schizophrenia. This population may have an underlying propensity to develop diabetes independent of antipsychotic treatment,[40] which is not reflected in current disease models. On the other hand, partial adherence to antipsychotic medications could diminish differential risks of diabetes and CHD linked to use of such medications. For example, in a 4-year study in the Veterans Affairs system among patients with schizophrenia and a medication claim for an antipsychotic, 39% had consistently good adherence, 43% were inconsistently adherent, and 18% had consistently poor adherence when good adherence was defined as a medication possession ratio ≥ 0.8 in all 4 years.[41]

In this study, the 2 treatment groups in the patient subsamples with fasting data were well matched in baseline levels of relevant variables. Nonetheless, randomization in the STAR treatment arms was limited by patients who did not complete the trial, did not have fasting laboratory values, or were missing other dimensions necessary for modeling. Although patient data from STAR did not include all required parameters for disease models, we were able to substitute data from relevant published studies. This substitution included data on patients with a family history of diabetes; however, it is a notable limitation of the study as it presumes that the family history would be similar among people with schizophrenia. Data on the proportions of smokers were also substituted with gender-specific prevalence rates from a Scottish population (males, 71%; females, 42%[25]), although these figures are consistent with gender-specific rates reported elsewhere in Europe (males, 79%; females, 48%[42]). In either case, all randomized arms were treated in the same way; therefore, use of data in this way should not impact on the relative risk of diabetes and CHD between treatments.

In conclusion, aripiprazole-treated patients had more favorable changes in lipids and body weight compared with SoC-treated patients. Modified versions of validated disease models support a reduction of risk of diabetes and CHD in patients receiving aripiprazole compared with SoC. Treatment with aripiprazole provides similar efficacy relative to other antipsychotic agents,[20,33,43,44] and, in addition, its favorable metabolic profile offers potential health benefits.

Drug names: aripiprazole (Abilify), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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