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ORIGINAL PAPER

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UK cost-consequence analysis of aripiprazole in schizophrenia: diabetes and coronary heart disease risk projections (STAR study)

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Abstract Patients with schizophrenia experience elevated rates of morbidity and mortality, largely due to an increased incidence of cardiovascular disease and diabetes. There is increasing concern that some atypical antipsychotic therapies are associated with adverse metabolic symptoms, such as weight gain, dyslipidaemia and glucose dysregulation. These metabolic symptoms may further increase the risk of coronary heart disease (CHD) and diabetes in this population and, subsequently, the cost of treating these patients' physical health. The STAR study showed that the metabolic side effects of aripiprazole treatment are less than that experienced by those receiving standard-of-care (SOC). In a follow-up study the projected risks for diabetes or CHD, calculated using the Stern and Framingham models, were lower in the aripiprazole treatment group. Assuming the risk of diabetes onset/CHD events remained linear over 10 years, these risks were used to estimate the difference in direct and indirect cost consequences of diabetes and CHD in schizophrenia patients treated with aripiprazole or SOC over a 10-year period. Diabetes costs were estimated from the UKPDS and UK T^2ARDIS studies, respectively, and CHD costs were estimated using prevalence data from the Health Survey of England and the published literature. All costs were inflated to 2007 costs using the NHS pay and prices index. The number of avoided diabetes cases (23.4 cases per 1,000 treated patients) in patients treated with aripiprazole compared with SOC was associated with estimated total (direct and indirect) cost savings of £37,261,293 over 10 years for the UK population. Similarly, the number of avoided CHD events (3.7 events per 1,000 treated patients) was associated with estimated total cost savings of £7,506,770 over 10 years. Compared with SOC, aripiprazole treatment may provide reductions in the health and economic burden to schizophrenia patients and health care services in the UK as a result of its favourable metabolic profile.

Key words aripiprazole · atypical antipsychotic · cost-effectiveness · diabetes · schizophrenia

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Introduction

Patients with schizophrenia experience elevated rates of morbidity and mortality, and have life expectancy approximately 20% shorter than the general popula-

tion [36], largely due to an increased incidence of cardiovascular disease (CVD) and diabetes [5, 6]. Previous studies have shown that there are several risk factors that contribute to the increased risk of CVD in schizophrenia, and a further multiplicative interrelationship between these individual risk factors may exist [46]. Individuals with schizophrenia are also more likely to smoke, take less exercise and have a more unhealthy lifestyle than the general population [15], which may further elevate CVD and diabetes risk.

There is currently a wide selection of atypical antipsychotic agents available in the UK [33], which now form the core treatment for schizophrenia [28]. These agents are associated with lower risk of short- and long-term neurological side effects than first-generation antipsychotic medications [28]. However, there is increasing concern that some atypical antipsychotic therapies are associated with adverse metabolic symptoms, such as weight gain [31], dyslipidaemia [28] and glucose dysregulation, which may further increase the risk of coronary heart disease (CHD) and diabetes in this population [44, 46]. As the atypical antipsychotics generally appear to have similar efficacy profiles [14, 28], it is important that their metabolic and cardiovascular impact should be considered when making treatment decisions [1, 33].

The CLAMORS study collaborative group assessed the prevalence of CHD using the Framingham risk equation (10-year risk for all CHD events [46]) in Spanish outpatients with schizophrenia, schizophreniform or schizoaffective disorder who received antipsychotic treatment for at least 12 weeks [4]. CHD risk was elevated to an average level seen in the Spanish general population who were 10–15 years older. A community population of patients with schizophrenia from the CATIE study showed a higher 10-year CHD risk compared with matched controls, as evidenced by higher prevalence of smoking, diabetes, hypertension and lower levels of high-density lipoprotein (HDL)-cholesterol [13].

Healthcare decisions for patients should also consider the economic benefits of side effects avoided when examining cost-effectiveness of treatment. The impact of schizophrenia on healthcare budgets is substantial, typically between 1.5 and 3% of the total national healthcare expenditure [24]. In comparisons among antipsychotic agents for the treatment of patients with schizophrenia, reduced costs are often achieved by lower expenditures for psychiatric hospitalization [42, 43]. Patient non-adherence to medication, largely due to treatment-related adverse events and patient dissatisfaction with treatment, leading to high relapse rates, is also believed to contribute significantly to costs [23]. To date, there has been limited examination of the potential costs associated with comorbid incidence of CHD and diabetes in the UK.

Aripiprazole is an atypical antipsychotic with partial agonist activity at dopamine D_2 receptors [27], with a pharmacological profile different from that of other antipsychotics. In a recent naturalistic European study (Schizophrenia Trial of Aripiprazole: STAR study) conducted across 12 European countries, aripiprazole was compared with standard-of-care (SOC) agents, where SOC consisted of physicians' selection of olanzapine, quetiapine or risperidone [22]. The results demonstrated a greater effectiveness for aripiprazole, as assessed by the Investigator Assessment Questionnaire (IAQ), the CGI-I scale and quality of life, compared with SOC. Aripiprazole also showed a minimal potential to adversely affect total cholesterol, low-density lipoprotein (LDL)-cholesterol, triglycerides, serum prolactin and weight gain, whereas patients treated with SOC had adverse changes in these parameters [22].

Metabolic data from the STAR study [22] and validated predictive models were used by Blonde et al. [3] to predict the long-term risks of diabetes and CHD for patients with schizophrenia receiving aripiprazole or SOC. In the analysis reported in this paper, the projected risk data were used to estimate associated costs of diabetes and CHD to the UK healthcare service.

Methods

Subjects

Patient data were derived from STAR, a 26-week prospective, multicentre, randomized, open-label trial conducted at 98 study centres in 12 countries throughout Europe during 2004–2005 [22]. Briefly, patients (aged 18–65 years) with a diagnosis of schizophrenia (according to DSM-IV criteria) were eligible for study entry if they were being treated within a community setting and their treating clinician judged that they required a change in, or initiation of, antipsychotic medication. To justify a change of antipsychotic medication, patients had to have symptoms that were not optimally controlled or side effects that indicated medication was not well tolerated. Exclusion criteria were as follows: suicidal risk, evidence of treatment resistance and administration of a long-acting antipsychotic within 3 weeks prior to randomization. The study was conducted in accordance with the Declaration of Helsinki and good clinical practices (GCP).

In total, 555 patients were randomized into one of two treatment arms in a 1:1 ratio to 26 weeks of treatment with aripiprazole (15–30 mg/day) or SOC (clinician's choice of olanzapine 5–20 mg/day, quetiapine 100–800 mg/day or risperidone 2–8 mg/day). Study completion rates with aripiprazole and SOC were 58% and 61%, respectively. Full details of the STAR study are reported elsewhere [22]. Fasting laboratory samples were available for approximately half of the study population (aripiprazole, 138/282 [48.9%]; SOC 131/266 [49.2%]) [22].

Metabolic assessments and risk predictions

Metabolic outcomes

In a follow-up study by Blonde et al. [3] risk factor data on metabolic outcomes from the STAR study [22] were used to project the incidence of diabetes and CHD over a 7.5-year and 10-year period, respectively, stratified by treatment. The primary endpoint for risk factor assessments was 26 weeks, using the last observation carried

forward (LOCF) in the safety sample, which was composed of all patients who received at least one dose of antipsychotic medication. Metabolic outcomes included mean changes from baseline in fasting total cholesterol, fasting HDL-cholesterol, fasting LDL-cholesterol, fasting triglycerides, fasting glucose and body weight [22].

Diabetes risk predictions

In the Blonde study [3] the projected incidence of diabetes (defined as treatment with insulin or oral hypoglycaemic agents or fasting blood glucose ≥6.9 mmol/l [18]) for a hypothetical cohort of 1,000 patients over a 7.5-year period was estimated per treatment arm using the Stern model from the San Antonio Heart Disease Study (SAHDS) [44]. Variables included age, gender, ethnicity, fasting glucose level, systolic blood pressure, fasting HDL-cholesterol level, body mass index, and parent or sibling with diabetes. Several adaptations to the Stern model were carried out as not all of the above variables were available from the STAR dataset. These included classifying all patients as White to fit the classification in the original SAHDS sample as non-Hispanic White or Mexican American (>96% of STAR patients were white) and use of rates for parent/sibling with diabetes in non-Hispanic white patients from the SAHDS sample [44]. As fasting status was variable in the STAR study [22], the prediction in this analysis was performed with fasting subjects only.

CHD risk predictions

Blonde et al. [3] projected the incidence of CHD (defined as risk of developing one of the following: angina pectoris, myocardial infarction or coronary disease death) in each treatment arm for a hypothetical cohort of 1,000 patients over a 10-year period using the Framingham risk equation [46]. Variables included age, LDL-cholesterol level, HDL-cholesterol level, systolic blood pressure, diabetes and smoking status, and were where possible derived from assessed values from the STAR study. LDL- and HDL-cholesterol values from the total study population were used in this analysis. Smoking status was not assessed in the STAR study, therefore, substituted rates of smoking by gender were based on a European sample of patients with schizophrenia (71% males, 42% females) [21].

Statistical analyses

The estimated incidences of diabetes and CHD are based on well-validated risk equations that use mean changes from baseline to Week 26 (LOCF) in metabolic parameters—fasting as appropriate (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, glucose and body weight), analysed by treatment group using an analysis of covariance (ANCOVA), with treatment and fasting status as main effects and baseline levels as covariate. Analyses were conducted for all patients in the safety sample (who received at least one dose of study medication) and for the sub-sample who had fasting values. Mean changes from baseline are reported as least squares mean values and as treatment differences with aripiprazole as the reference. P values < 0.05 were considered significant for metabolic outcomes.

Patients with missing baseline and/or endpoint risk factors or patients with pre-existing diabetes were excluded from the risk predictions. The number needed to treat (NNT) is calculated as the number of patients who need to be treated with aripiprazole to prevent one diabetes/CHD case. The NNT (1/ARD [absolute risk difference]) was calculated [38] and the results extrapolated to a hypothetical population of 1,000 patients.

Cost impact assessments

Risk predictions for diabetes and CHD were used to estimate associated costs of treating these conditions to the UK healthcare service. Published data was used to estimate the annual 2007 indirect and direct costs of treating diabetes and CHD per patient as outlined below. Schizophrenia prevalence data for the UK was then used to estimate the cost saving of avoided cases in the UK population.

Inflation calculations

Direct and indirect costs per patient per year for both diabetes and CHD were inflated from the date of the published cost calculation to 2007 prices (date of current analyses). Inflation rates were calculated based on the average yearly percent increase in the NHS pay and prices index [10].

Diabetes cost calculations

Direct costs due to diabetes were projected based on the UKPDS study in which mean direct diabetes costs per patient per year (inpatient and outpatient costs, and costs related to macrovascular, microvascular and eye-related complications) were estimated at £947 for 1997 [9]. Costs for 1997 were inflated to give an estimate of mean cost per patient per year for 2007 as £1,393 calculated using the NHS pay and prices index (1997–2007) [10].

Indirect costs per patient per year of lost employment for patients and carers combined (<65 years of age) due to diabetes were projected based on 1998 values from the UK T^2ARDIS study [17]. Mean indirect costs per patient for 1998 (£1,222) were inflated to give an estimate of mean indirect cost per patient per year for 2007 (£1,771) calculated using the NHS pay and prices index (1998–2007) [10].

CHD cost calculations

Direct and indirect costs due to CHD were projected based on a study by Luengo-Fernández et al. [29] in which mean CHD costs per patient per year were estimated for 2004 (direct per patient per year costs were estimated as £1,367.02 and indirect per patient per year costs were £2,203.71). However, no UK CHD prevalence rates are given in this publication, and prevalence for the population aged over 16 years was therefore estimated from two other sources. The Health Survey of England 2003 reported the total 2003 UK CHD prevalence for men as 7.4% and for women as 4.5% [40], which applied to national population statistics for 2003 gives UK prevalence estimates of CHD of 1,709,800 men and 1,113,100 women. For cost calculations the assumption was made that the CHD prevalence (after adjustment for age) estimated in 2003 would remain stable through 2007. Costs for 2004 were inflated to give an estimate of mean cost per patient per year for 2007. Inflated direct costs per patient per year were, therefore, £1,543.72 and inflated indirect costs per patient per year £2,488.56.

Avoided case cost calculations in the schizophrenia population

Based on an estimated UK prevalence of schizophrenia of 1% [33] the total schizophrenia population in 2007 was 605,000. The predicted avoided case calculations performed by Blonde et al. [3] for diabetes (fasting sample) and CHD (total study sample) were applied to the estimated schizophrenia population. The direct and indirect cost savings over 10 years were calculated by multiplying the total number of avoided cases by the cost per patient per year for either diabetes or CHD. This calculation made the assumption that the number of avoided cases per year was linear and was maintained over the 10-year period. Cost savings were then discounted by an annual rate of 3.5%. [34].

Sensitivity analysis and external validation

In order to test the sensitivity of our findings to the input assumptions used in cost calculations, a number of deterministic sensitivity analyses were performed. One-way sensitivity analyses were undertaken to assess the impact of varying schizophrenia prevalence (0.8–1.2%), estimated yearly costs per diabetes or CHD event (±20%), and the discount rate used (0–6%) [34] on the total (direct and indirect) cost savings over 10 years (calculated as outlines above).

Results

Patient demographics and baseline characteristics

The baseline demographics and characteristics of patients are presented in Table 1. Patient characteristics (Table 1) and metabolic parameters at baseline (Table 2) were comparable between treatment groups and also with the CUtLASS study sample [19]. The CUtLASS study population is viewed as broadly representative of a treated sample of patients with schizophrenia in the UK [19] and the US [13, 28, 30], and therefore comparable with the populations in which the Stern and Framingham models are validated. Characteristics of the total safety sample (n = 546) and the fasting sub-sample (n = 262) were similar across treatment groups.

Metabolic outcomes

Differences in metabolic risk factor levels by treatment from baseline to 26 weeks are presented in Table 3. A significantly lower proportion of patients in the aripiprazole group had potentially clinically relevant changes in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride levels and body weight, compared with the SOC group ($P < 0.05$; Table 3). There was no significant difference observed between SOC and aripiprazole in fasting glucose at 26 weeks (Table 3).

Diabetes risk predictions (Stern model)

In a hypothetical cohort of 1,000 patients, aripiprazole treatment was predicted using the Stern model to result in 23.4 fewer onsets of diabetes over 7.5 years

Table 1 Demographic characteristics and psychiatric history at baseline in standard-of-care and aripiprazole groups

Baseline characteristics	Standard-of-care (n = 271)	Aripiprazole (n = 284)	Total (n = 555)
Age, mean ± SD years	38.3 ± 11.1	38.1 ± 10.8	38.5 ± 10.9
Gender, *n* (%)			
Male	163 (60)	169 (60)	332 (60)
Female	108 (40)	115 (41)	223 (40)
Race, *n* (%)			
White	262 (96.7)	274 (96.5)	536 (96.6)
Black	1 (0.4)	3 (1.1)	4 (0.7)
Asian	6 (2.2)	3 (1.1)	9 (1.6)
Other	2 (0.8)	4 (1.4)	6 (1.1)
Body weight mean ± SD kg	81.0 ± 17.0	80.4 ± 17.5	80.7 ± 17.2
Baseline BMI, mean ± SD kg/m^2	27.3 ± 5.1	27.2 ± 5.1	27.2 ± 5.1
Type of schizophrenia, *n* (%)			
Disorganised	32 (11.8)	24 (8.5)	56 (10.1)
Catatonic	4 (1.5)	3 (1.1)	7 (1.3)
Paranoid	172 (63.5)	189 (66.5)	361 (65.0)
Residual	36 (13.3)	31 (10.9)	67 (12.1)
Undifferentiated	27 (10.0)	37 (13.0)	64 (11.5)
Duration of illness, mean ± SD years	10.7 ± 9.6	10.3 ± 9.6	11.5 ± 9.5
Age at first hospitalization for schizophrenia, mean ± SD years	28.7 ± 8.7	28.3 ± 8.5	28.5 ± 8.6

Adapted from Kerwin et al. 2007 [22] (Reproduced with permission of Elsevier Masson SAS)
SD standard deviation, *BMI* body mass index

Table 2 Metabolic parameters at baseline among patients receiving standard-of-care or aripiprazole

Metabolic parameters	Standard-of-care	Aripiprazole
Total cholesterol, mean ± SD mmol/l	5.45 ± 1.1 (n = 245)	5.51 ± 1.1 (n = 262)
LDL-cholesterol, mean ± SD mmol/l	3.23 ± 1.0 (n = 245)	3.17 ± 0.24 (n = 261)
HDL-cholesterol, mean ± SD mmol/l	1.32 ± 0.4 (n = 242)	1.29 ± 0.38 (n = 262)
Triglycerides, mean ± SD mmol/l	2.20 ± 1.6 (n = 241)	2.15 ± 1.58 (n = 261)
Fasting glucose, mean ± SD mmol/l	5.39 ± 1.06 (n = 115)	5.42 ± 1.06 (n = 114)
Body weight, mean ± SD kg	81.0 ± 17.0 (n = 269)	79.9 ± 17.5 (n = 284)

SD standard deviation, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein

Table 3 Mean change from baseline in metabolic risk factor levels at 26 weeks, among patients receiving standard-of-care or aripiprazole

Metabolic parameters	Standard-of-care	Aripiprazole	Difference	*P* value
Total cholesterol, mean ± SD mmol/l	−0.20 ± 0.29	−0.53 ± 0.29	−0.33	<0.001
LDL-cholesterol, mean ± SD mmol/l	−0.15 ± 0.64	−0.35 ± 0.62	−0.19	<0.001
HDL-cholesterol, mean ± SD mmol/l	0.010 ± 0.18	0.052 ± 0.18	0.042	0.028
Triglycerides, mean ± SD mmol/l	−0.15 ± 1.00	−0.52 ± 1.02	−0.38	<0.001
Fasting glucose, mean ± SD mmol/l	0.18 ± 0.08	0.011 ± 0.08	0.17	0.146
Body weight, mean ± SD kg	1.40 ± 5.01	−1.30 ± 6.42	−2.7	<0.001

SD standard deviation, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein

Table 4 Projected diabetes risk over 7.5 years in aripiprazole and standard-of-care groups, calculated using Stern model

Risk Measurement	Aripiprazole (n = 108)	SOC (n = 111)	Absolute risk difference (NNT)
Baseline	0.1515	0.1513	
Post-baseline	0.1507	0.1739	
Change from baseline	−0.0008	0.0226	−0.0234 (43)

Predictions limited to subsample of fasting subjects to be consistent with Stern model specifications
SOC standard-of-care, *NNT* number needed to treat

relative to SOC treatment. The projected difference in risk was −0.0234 (Table 4); and the NNT was 43 [3].

CHD risk predictions (Framingham model)

In a hypothetical cohort of 1,000 patients, aripiprazole treatment was predicted using the Framingham risk algorithm to result in 3.7 fewer CHD events over 10 years relative to SOC treatment (Table 5). The projected risk difference in the total study sample was −0.0037 and the NNT was 270 [3].

Associated cost impact of diabetes and CHD risk predictions

When treating schizophrenia patients with aripiprazole compared with SOC the accumulated avoided direct and indirect costs for diabetes in a 10-year period are estimated to be £16,405,246 and £20,856,047, respectively, (Fig. 1a). Therefore, a total of £37,261,293 may be saved on projected diabetes events over a 10-year period.

Similarly, the accumulated avoided direct and indirect costs for CHD in a 10-year period are estimated to be £2,873,892 and £4,632,878, respectively (Fig. 1b). Therefore, a total of £7,506,770 may be saved on projected CHD events over a 10-year period.

Sensitivity analysis showed that varying the discount rate used from 0–6% caused the total avoided costs of diabetes and CHD over 10-years to vary between £33 M–£45 M and £7 M–£9 M, respectively. As would be expected, lowering the prevalence of schizophrenia to 0.8% caused total costs savings over 10-years to decrease (£30 M for diabetes and £6 M for CHD) while increasing the prevalence of schizophrenia to 1.2% caused total costs savings over 10-years to increase (£45 M for diabetes and £9 M for CHD). Varying the yearly costs per diabetes case (±20%) caused direct costs for diabetes in a 10-year period to range between £13 M and £20 M and the indirect costs to range between £17 M and £25 M. Varying the yearly costs per CHD case (±20%) caused direct costs for CHD in a 10-year period to range between £2 M and £3 M and the indirect costs to range between £4 M and £6 M.

Discussion

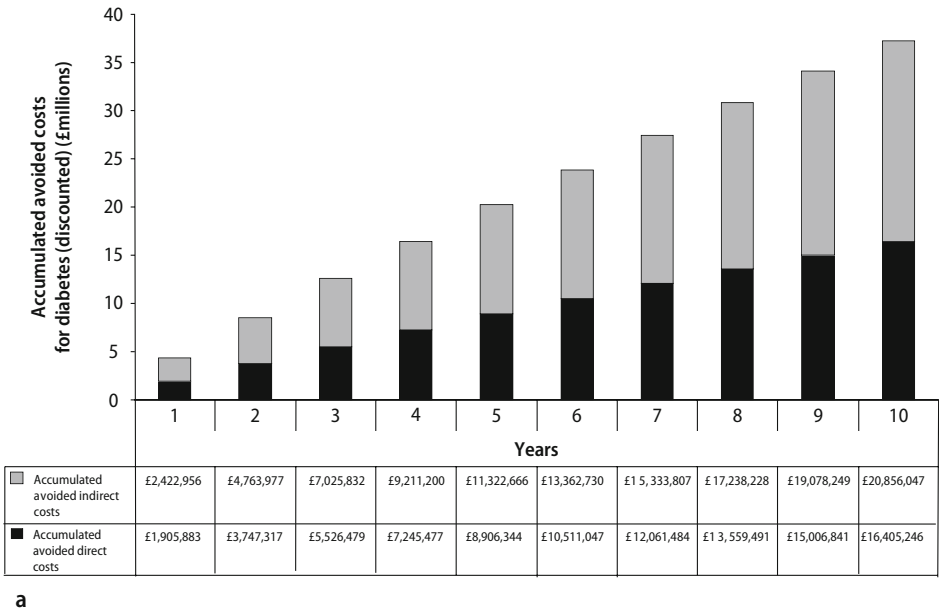
This projected risk analysis of metabolic data using modified Stern and Framingham models showed that, relative to SOC antipsychotic treatment, aripiprazole treatment was predicted to result in fewer onsets of diabetes over 7.5 years and fewer incidences of CHD over 10 years. Cost projections suggest that, compared with SOC, aripiprazole may be associated with long-term cost savings to the UK health service as a result of reduced incidences of treatment-related diabetes and CHD in schizophrenia patients [2].

The Framingham model that was used to predict the long-term risk of CHD may be more conservative than the Stern risk equation for diabetes. Hence, the

Table 5 Projected coronary heart disease (CHD) risk over 10 years in aripiprazole and standard-of-care groups, calculated using Framingham model

Risk measurement	Aripiprazole (n = 256)	SOC (n = 237)	Absolute risk difference (NNT)
Baseline	0.0601	0.0629	
Post-baseline	0.0565	0.0630	
Change from baseline	−0.0036	0.0001	−0.0037 (270)

Predictions performed on total study sample
SOC standard-of-care, *NNT* number needed to treat



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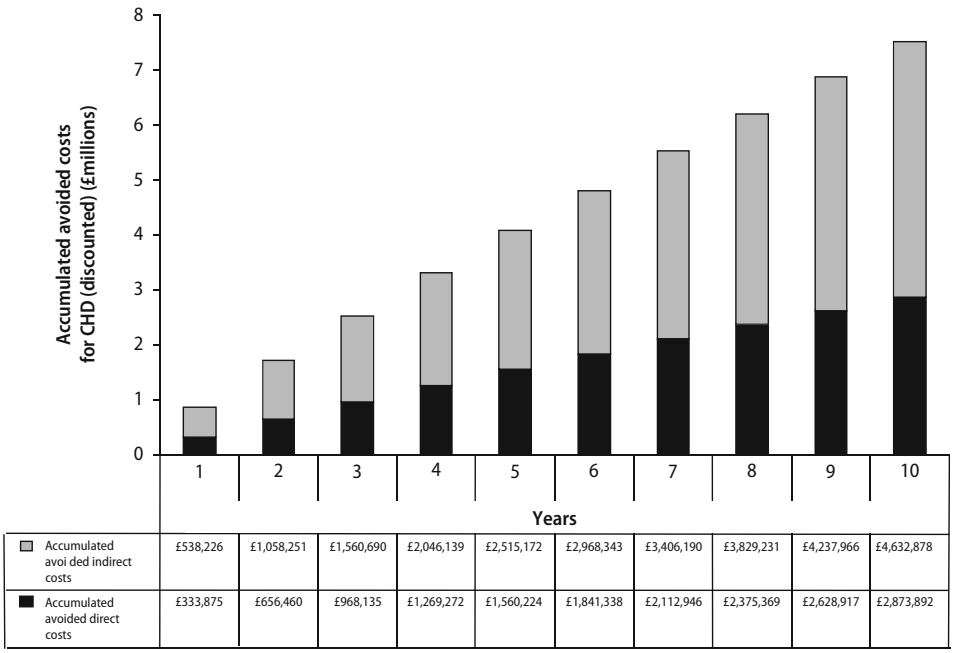

b

Fig. 1 Accumulated avoided direct and indirect costs (discounted) with aripiprazole treatment compared with standard-of-care for **a** diabetes and **b** coronary heart disease (*CHD*)

predicted reduction in new cases of diabetes and the associated cost saving with aripiprazole treatment vs. SOC (23.4 fewer cases; £37,261,293 cost saving) is predicted to be higher than for CHD (3.9 fewer CHD events; £7,506,770 cost saving).

The models adopted in this analysis are subject to a number of limitations and assumptions. (1) Both the Framingham and Stern models assume that the antipsychotic medication is unchanged over the medication period when making risk predictions. (2) The risk levels were calculated using data from the 6-month STAR study [22]; the short-term nature of this study suggests the differences in LDL- and HDL-cholesterol and thus the risk calculations are likely to be underestimated. While changes in cholesterol in a 1 year study of aripiprazole versus olanzapine were larger than in the STAR study, much of the change observed at 52 weeks is present at Week 28 [8]. (3) Metabolic levels were also assumed to be stable for the modelling period, however, this may lead to an under- or over-estimate of the risk calculations for patients who initiate statin or blood pressure treatments. Switching between antipsychotics should not affect the metabolic levels in the risk calculations as the SOC data are a weighted average between three treatments assuming that patients were equally switched between SOC medications. (4) CHD and diabetes risk may vary between individual SOC treatments (olanzapine,

quetiapine and risperidone) but the design of the original STAR study on which this analysis was based precludes direct comparison of aripiprazole to each of the SOC treatments. However, the similar directional change in the individual SOC treatment arms for diabetes and CHD risk supports the grouping of all three drugs into one SOC arm for the purpose of this analysis [3]. (5) Treatment with aripiprazole was assumed to provide similar efficacy relative to other SOC treatments [8, 22, 39, 45]. Inclusion of cost calculations potentially resulting from differences in efficacy between agents was beyond the scope of this analysis. (6) The cost analysis does not take into account the cost of antipsychotic medications due to the unpredictable introduction of generic medications into the UK market. (7) It is assumed that the prevalence of schizophrenia and the costs per case remain constant over time. (8) The cost calculations assume that the avoided event probabilities remain linear for the 10-year period over which they are calculated.

This analysis is based on the STAR naturalistic study [22] and therefore, reflects risk and costs associated with a population that more closely represents real life than might be expected from patient populations in randomized clinical trials. It should, however, be noted that the STAR study excluded patients with treatment-resistant schizophrenia, and the results presented here may not generalize to these patients. The physical health and metabolic outcomes are consistent with previous studies reporting the differential effects of antipsychotics. The prevalence of metabolic syndrome is often higher in schizophrenia patients treated with some atypical antipsychotics, notably clozapine, olanzapine, quetiapine and risperidone, depending on the rigour of the study design [11, 12]. The incidence of metabolic syndrome has been reported to be significantly lower in patients treated with aripiprazole than in those treated with olanzapine [25]. However, a new diagnosis of diabetes does not usually result in antipsychotic medication changes [26]. Schizophrenia-related costs were not significantly different for patients treated with olanzapine compared with those treated with risperidone [41].

The mean annual direct per patient costs for type II diabetes of £947 utilized in this analysis based on 1997 prices and data from the UKPDS study are slightly lower than those observed in previous studies. An analysis of direct type II diabetes-related direct medical costs across eight European countries reported an average yearly direct cost per patient of EUR 2,834, and in the UK subgroup an average yearly direct cost per patient of EUR 2,214 based on 1999 prices [20] (equivalent to £1,667). Similarly, the average annual per patient direct medical cost for a Swedish type II diabetes population was 25,000 SEK based on 1998 prices [16]. The cost savings calculated in this analysis, based on per patient costs from the UKPDS study, may therefore represent a conservative estimate. Had the costs been calculated from the UK data in the CODE-2 study [20] the avoided indirect costs for diabetes would be higher at approximately £26,000,000 compared with a more conservative £16,405,246 when using the UKPDS data.

For CHD the mean annual per patient direct cost of £1,367 (based on 2004 prices) used in this analysis was comparable to a similar analysis in Sweden in which the mean direct costs during the year after a clinical event were SEK 41,000 for congestive heart failure and SEK 96,000 for stroke [47].

The metabolic effects associated with atypical antipsychotics are of current interest, as they are predictors of cardiovascular morbidity and mortality in patients with schizophrenia. Current guidelines recommend that the long-term health consequences of antipsychotic-related adverse events should be considered when making treatment decisions [35]. As shown in this analysis, the favourable metabolic profile of aripiprazole has potential long-term health benefits, combined with economic benefits to health care providers, making considered prescribing of significant importance. It should also be considered that atypical antipsychotics are a recommended treatment option for patients with bipolar disorder [32]; a patient population also at increased risk of diabetes [7] and CVD [37]. Thus the favourable metabolic profile of aripiprazole may also translate into potential cost-benefits in the treatment of bipolar disorder and warrants further investigation.

As a result of its favourable metabolic profile, aripiprazole treatment has the potential to provide reductions in the health and economic burden to schizophrenia patients and psychiatric healthcare services in the UK. More detailed cost-effectiveness analyses of the atypical antipsychotics are recommended.

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Conflict of interest AB has received honoraria for lectures relevant to this area from Bristol-Myers Squibb, Otsuka, Sanofi-Aventis and AstraZeneca. HM has received honoraria for lecturing and advisory work from Bristol-Myers Squibb, Otsuka, Janssen-Cilag and Wyeth. JYL is an employee of Otsuka Pharmaceuticals. GI and MVB are employees of Bristol-Myers Squibb. MK has received financial support for undertaking research, lecturing, and advisory work from Eli Lilly, Bristol-Myers Squibb, Organon and the Department of Health for England.

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