Cost-effectiveness of atorvastatin in the prevention of cardiovascular events in diabetic patients: A French adaptation of CARDS

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Summary

Introduction. — We estimated the cost-effectiveness of atorvastatin in the primary prevention of cardiovascular events in patients with type 2 diabetes using data from the Collaborative AtorVastatin Diabetes Study (CARDS).

Methods. — A total of 2838 patients aged 40–75 years with type 2 diabetes and no documented history of cardiovascular disease and without elevated low-density-lipoprotein cholesterol were recruited in the UK and in Ireland. Patients were randomly allocated to atorvastatin 10 mg daily \( (n = 1428) \) or placebo \( (n = 1410) \) and were followed up for a median of 3.9 years. Direct treatment costs and effectiveness were analysed to provide estimates of cost per event avoided and cost per life-year gained over the trial period and over a patient’s lifetime.

Results. — The incremental cost-effectiveness ratio over the trial period was estimated to be €3862 per clinical event avoided. Over the patient’s lifetime, the incremental cost per life-year gained was €2506 when considering cardiovascular deaths, and €1418 per year when considering all-cause death.

Conclusions. — Primary prevention of cardiovascular disease with atorvastatin is cost-effective in patients with type 2 diabetes, with the incremental cost-effectiveness ratio for this intervention falling within the current acceptance threshold.

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Introduction

Diabetic patients are at high risk of cardiovascular morbidity and mortality [1]. Since the introduction of statins 20 years ago, their indications have broadened with the emergence of data from numerous large randomized clinical trials. Now their approved indications include treatment of elevated low-density-lipoprotein (LDL) cholesterol, secondary prevention of cardiac events, and primary prevention of cardiac events in large subgroups of the population, including those with diabetes and at least one additional risk factor and without elevated LDL cholesterol. Atorvastatin was recently approved for the latter indication in France, based on the results of the Collaborative AtoRvastatin Diabetes Study (CARDS) [2—4]. This clinical trial was performed under the aegis of the UK Department of Health and was coordinated by University College London. The trial was designed to demonstrate the efficacy of atorvastatin in the primary prevention of cardiac events in patients presenting with diabetes and without elevated LDL cholesterol.

While there is no question as to the efficacy of atorvastatin in this group, it is important to evaluate its cost-effectiveness because of the large number of individuals who could benefit from the product. The French Transparency Commission estimated this target population to be approximately 600,000 in France [5]. The cost-effectiveness of atorvastatin has already been studied in Spain [6] and in the United Kingdom [7], but healthcare systems and medical expenses vary widely between countries. Therefore, the objective of the present study was to estimate its cost-effectiveness in the primary prevention of cardiac events in a French diabetic population without elevated LDL cholesterol.

Methods

This study is based largely on data from the CARDS clinical trial, which has been described in detail elsewhere [2—4]. In brief, a population of UK patients was randomly allocated to placebo or atorvastatin (10 mg daily). Patients were eligible for inclusion if they were diabetic, had no history of cardiac events, had an LDL cholesterol level lower than 4.14 mmol/L, and had at least one associated risk factor (retinopathy, albuminuria, current smoking or hypertension). The median duration of follow-up was 3.9 years in both groups. The risk reduction of cardiovascular events was estimated at 37% (95% confidence interval 17—52; \( P < 0.001 \)) for atorvastatin, and treatment of 1000 patients could avoid 37 major events each year. Treatment was associated with a mortality reduction of 27% (\( P = 0.059 \)) during the follow-up period. No significant side-effects were observed in either group and the trial was stopped prematurely because of the significance of efficacy in the second planned intermediary analysis.

The present cost-effectiveness study was carried out according to French guidelines [8,9]. The primary endpoints were the number of clinical events observed during the trial and the life expectancy of patients extrapolated to the lifetime of a similar population, comparing atorvastatin 10 mg daily to usual care without systematic atorvastatin treatment.

The number of cardiac events was extracted from the main article [4] and the clinical report. Owing to statistical considerations, the first event of one type was considered per patient in the article, which could lead to an underestimation of the economic difference between groups because patients with a first event are more likely to present with a second.

Life-expectancy estimates were calculated using the DEALE method [10]. This approach allows us to estimate the life expectancy of a particular population, taking into account the decrease in life expectancy of diabetic patients compared with that of the general population, and was based on data from Gu et al. [11]. In the UK Prospective Diabetes Study (UKPDS), the life expectancy of diabetic patients with a mean age of 54 was approximately 20 years [12,13].

The following calculations were performed as follows:
Atorvastatin in the prevention of cardiovascular events in diabetic patients

Table 1  Standard costs of cardiac events observed during CARDS inflated to 2007 prices.

<table>
<thead>
<tr>
<th>Cardiac event</th>
<th>Cost of hospitalization (€2007)</th>
<th>Cost post-hospitalization (€) 1st year</th>
<th>Total cost (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>5014</td>
<td>11,098</td>
<td>16,112</td>
</tr>
<tr>
<td>Fatal myocardial infarction</td>
<td>4709</td>
<td>—</td>
<td>4709</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>12,403</td>
<td></td>
<td>12,403</td>
</tr>
<tr>
<td>Stroke</td>
<td>6057</td>
<td>10,287</td>
<td>16,344</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>7167</td>
<td>—</td>
<td>7167</td>
</tr>
<tr>
<td>Angina</td>
<td>4404</td>
<td>3003</td>
<td>7407</td>
</tr>
<tr>
<td>Non-fatal cardiac arrest</td>
<td>9890</td>
<td>—</td>
<td>9890</td>
</tr>
<tr>
<td>Sudden death</td>
<td>7350</td>
<td>—</td>
<td>7350</td>
</tr>
</tbody>
</table>

- yearly mortality rate according to age and sex ($\mu_{\text{ASR}}$) calculated from French life-expectancy tables [14] ($\text{LE}_{\text{ASR}}$) with $\mu_{\text{ASR}} = 1/\text{LE}_{\text{ASR}}$;
- mortality rate specific to diabetes ($\mu_{D}$);
- calculation of the specific life expectancy of the diabetic population ($\text{PSLE}$) $\text{PSLE} = 1/(\mu_{\text{ASR}} + \mu_{D})$.

where $\text{ASR} =$ age—sex ratio, LE = life expectancy, and PSLE = patient-specific life expectancy.

The characteristics of the CARDS population were included, namely median age 63 years, seven-year history of diabetes, 32% women, and a follow-up duration of four years. The final estimate was applied to deaths avoided to estimate the total number of additional life years of patients in the atorvastatin group. The population of interest corresponded to the one included in the trial as well as the time horizon (3.9 years). The economic perspective concerned the French Sickness Fund because all patients in France who present with diabetes are fully reimbursed as their condition is categorized as chronic (affection de longue durée: long term disease) [15].

Considered costs were those of the statin — investigators could prescribe statins according to their clinical judgement — and the costs of treatment for cardiac events. Neither the cost of follow-up nor the indirect costs were taken into account because statin management does not add high costs to the current management of diabetic patients and no relevant information was available for indirect costs.

The information available from CARDS on resources used was valued using French standard costs. The unit costs of treating cardiac events in diabetic patients were those published recently [16] based on an analysis of the national hospital discharge database (programme médicalisé des systèmes d’informations [PMSI]) and the published literature. These estimates were inflated using the healthcare service price index [17], and are presented in Table 1.

The costs of statin treatment were based on their use in the CARDS study in both groups. Costs were calculated using 2007 official tariffs, and for statins other than atorvastatin were based on the market share of the different dosages and types available (including generic and brand name products). The rates of statin use according to year of follow-up in CARDS is shown in Fig. 1. No discount rate was applied to these costs because of the relatively short duration of the study and mainly because of the lack of information on event chronology.

Incremental cost-effectiveness ratios were calculated with the criteria defined above (all cardiac events and per life-year gained) and using the calculated costs. Sensitivity
analyses were performed by calculating cost-efficacy ratios for first events only (based on the results of the article) and for life-year gained in the clinical trial period (two years lost per fatal event, on average).

### Results

#### Clinical endpoints

The number of cardiac events observed during the CARDS trial is shown in Table 2. Of the 1428 patients in the atorvastatin group, 83 presented at least one cardiac event as defined by the protocol, compared with 127 of 1410 patients in the placebo group. The risk reduction was calculated at 37% \((P<0.001)\). Separately assessed, atorvastatin reduced the risk of acute coronary heart disease by 36%, coronary revascularization by 31%, and stroke by 48%. Atorvastatin also reduced mortality by 27% \((P=0.059)\). Secondary events were less frequent in the atorvastatin group \((n=23)\) than in the placebo group \((n=38)\).

Using the DEALE method, diabetic patients with a mean age of 67 years (at the end of CARDS follow-up) had an average life expectancy of 7.55 years.

#### Costs

Average costs per patient of statins and management of cardiac events are presented in Table 3. The extra cost of the atorvastatin strategy was estimated at €165 per patient. This extra cost was due mainly to the additional cost of statins (+€727), but was offset partly by the lower costs associated with treatment of cardiac events (−€562) in the atorvastatin group.
Cost-effectiveness

The calculated cost-effectiveness ratios are presented in Table 4. The incremental cost-efficacy ratios of atorvastatin were estimated at €3862 per cardiac event avoided (€165 divided by 4.27% of cardiac events avoided), at €18,920 per cardiovascular death avoided (€165 divided by 0.87%), and at €10,704 per death avoided (€165 divided by 1.54%). Based on an average benefit of 7.5 years per avoided death, costs per life gained were, respectively, €2506 for cardiovascular death and €1418 for all-cause death.

Sensitivity analyses

The results of the sensitivity analyses are given in Table 5. The extra cost of the atorvastatin strategy when taking into account only the first events was €337 per patient due to a lower number of events avoided. Costs per life-year gained were higher when considering only the lifetime benefit within the clinical trial period.

Discussion

The results from the CARDS study [2—4] demonstrated the efficacy of atorvastatin in the primary prevention of cardiovascular events in diabetic patients. The results of our study show that atorvastatin appears to be cost-effective in the French setting.

Our study is subject to certain limitations. First, we applied standard costs to clinical events rather than valuing the direct resources used in the CARDS study. The latter approach was used in the UK economic study [7], as the researchers used data that was relevant for their own healthcare system. Nevertheless, French hospital costs are driven by the diagnosis-related group system, and the use of hospital daily cost does not provide the best estimate for cardiovascular-event costs. Our approach of using standard costs based on national estimates avoided the main problem associated with estimated costs based on data collected, i.e. the inclusion of outliers, which could have biased the results. Fernandez de Bobadilla et al. [6], in a Spanish cost-effectiveness study, used a design similar to ours.

The second limitation is that the CARDS study was stopped prematurely and extrapolation of time was necessary to estimate the efficacy in terms of life expectancy. We chose to estimate the cost-efficacy ratios on the basis of resources consumed during the clinical trial, whereas British researches extrapolated both lifetime treatment with atorvastatin and efficacy. Our main concern about this design is that, as shown in Fig. 1, a large proportion of patients in the placebo arm will use statins and this proportion could increase dramatically over time. As a consequence, we preferred to use costs and efficacy based on the trial period.

The British study [7] was performed from the perspective of a unique healthcare purchaser – the National Health Service – and included only healthcare costs. They authors used two time horizons, the period of the trial and the patient’s lifetime. Time extrapolation was based on the assumption that patients on atorvastatin would be treated until they died, and that the cumulative survival difference observed in CARDS would continue over time. The authors calculated three endpoints: cardiac events and strokes (primary endpoints), any cardiovascular event (including other acute coronary heart disease events, transient ischaemic attack, peripheral vascular diseases, etc), and any adverse events (including all-cause death). Costs were based on resource consumption during the trial period (medications, visits, examinations, and hospitalizations) and standard costs were applied. Results that are strictly comparable with our study estimates were as follows: (1) cost per event avoided for the first cardiac event, with our estimate of €10,555 to be compared with £7608 (£10,879 using their exchange rate of £1.43 per £); and (2) cost per life-year gained, with our estimate of £2506 to be compared with £2755 (£3939) per life-year gained in the UK study. The difference can be explained by the additional cost of atorvastatin in the treated group and a longer life-expectancy due to this treatment.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Cost-effectiveness ratios of atorvastatin versus usual care according to endpoint criteria.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events avoided per patient</td>
<td>Cost per event avoided (€)</td>
</tr>
<tr>
<td>All cardiac events</td>
<td>165</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>0.0087</td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.0154</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Sensitivity analyses.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events avoided per patient</td>
<td>Cost per event avoided (€)</td>
</tr>
<tr>
<td>All cardiac events</td>
<td>337</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>0.0087</td>
</tr>
<tr>
<td>All-cause [ok?] death</td>
<td>0.0154</td>
</tr>
</tbody>
</table>
The Spanish study [6] was based on a model that mimicked the clinical trial results and extrapolated the life expectancy of patients according to the occurrence of an event (or not) with the published results. Standard costs of events were then applied. The authors found a cost per life-year gained of €5886. This higher estimate is due mainly to the higher cost (+50%) of atorvastatin in Spain at the time the study was conducted.

The results of these three studies, despite their different study designs, offer similar findings to our own: that atorvastatin is cost-effective and should be recommended in this population. In conclusion, therefore, primary prevention of cardiovascular disease with atorvastatin is a cost-effective intervention in French patients with type 2 diabetes, with the incremental cost-effectiveness ratio for this intervention falling within the current acceptance threshold, irrespective of the assumptions underlying the calculations.

References