

A Health Economic Model to Assess the Long-Term Effects and Cost-Effectiveness of Orlistat in Obese Type 2 Diabetic Patients

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OBJECTIVES — Obesity is a common condition in type 2 diabetic patients. Treating obesity may enhance hypoglycemic treatment and contribute to the reduction of long-term microvascular and macrovascular complications. Orlistat reduces cardiovascular risk factors in obese type 2 diabetic patients. The objectives of this study were to estimate the long-term clinical consequences of this weight loss and the resulting cost-effectiveness of treating obese type 2 diabetic patients with orlistat.

RESEARCH DESIGN AND METHODS — A Markov model was developed to predict, over a 10-year period, the complication rates and mortality with and without a 2-year orlistat treatment, assuming a 5-year catch-up period after treatment. A stepwise approach was used to obtain the clinical data. First, the impact of weight loss with orlistat on HbA_{1c}, blood pressure, and cholesterol was assessed; then, the impact on mortality and micro- and macrovascular complications of decreasing these risk factors was applied. Four subgroups were studied based on the presence of risk factors.

RESULTS — Cost-effectiveness varies between 3,462 Euro/life-year gained (LYG) for obese diabetic patients with hypertension and hypercholesterolemia and 19,986 Euro/LYG for obese diabetic patients without other risk factors. The latter result is not robust according to sensitivity analyses.

CONCLUSIONS — Our results suggest that orlistat is cost-effective in the management of obese type 2 diabetic patients, especially in those with the presence of hypercholesterolemia and/or hypertension. Evidence on longer-term benefits of orlistat (>2 years) will be of importance for future decision-making.

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Obesity causes an enormous burden for public health. For instance, in Belgium, 49% of men and 28% of women have a BMI between 25 and 30 kg/m², indicating overweight, and 14% of men and 13% of women have a BMI >30 kg/m², indicating obesity (1). In the U.S.,

these figures are even higher: 24.7% of women and 19.6% of men are obese (2). Type 2 diabetes is strongly associated with obesity. The lifetime risk of acquiring type 2 diabetes is ~50% in subjects with morbid obesity (3). Wolf et al. (4) reported that 63.5% of type 2 diabetic pa-

tients have a BMI ≥ 29 kg/m². Diabetes is a major risk factor for microvascular and macrovascular disease and will thus decrease life expectancy. Losing weight in obese diabetic patients may enhance hypoglycemic treatment and may even help patients to become normoglycemic or impaired glucose tolerant, consequently decreasing the risk for vascular diseases (5). However, whereas weight loss yields important benefits, recidivism is high (6). Hence, benefits may be lost over time.

Orlistat (Xenical), a gastrointestinal lipase inhibitor that reduces dietary fat absorption by ~30%, is an important aid in obtaining and maintaining weight loss. Trials in obese diabetic patients have proven that orlistat reduces cardiovascular risk factors such as high HbA_{1c}, LDL cholesterol, and blood pressure levels and may hence avoid complications and save lives (5,7).

Treatment of all obese type 2 diabetic patients with orlistat will involve an investment with regard to the drug budget. On the other hand, the improvement of the general prognosis of obese patients may lead to some savings and a gain in life expectancy. For instance, in the U.K. Prospective Diabetes Study (UKPDS), it was shown that reducing HbA_{1c} levels in obese diabetic patients lead to a reduction in morbidity and mortality and proved to be cost-effective (8,9).

The objective of this study was therefore to assess the cost-effectiveness of orlistat in these patients. Because there are currently no long-term data on orlistat in these patients, a model approach was required to assess the longer-term effects, which is a recommended approach in many disease areas (10–14). Therefore, a Belgian population of obese type 2 diabetic patients was chosen as a case. The resulting cost-effectiveness (cost per life-year gained [LYG]) of orlistat was calculated in different subtypes of patients, depending on the presence or absence of hypertension and/or hypercholesterolemia.

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Abbreviations: AHT, arterial hypertension; HHS, Helsinki Heart Study; LY, life year; LYG, LY gained; MI, myocardial infarction; UKPDS, U.K. Prospective Diabetes Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—Yearly event rate in obese diabetes*

Treatment group	HbA _{1c} RR (%)	Total death	Nonvascular death	Macrovascular complications									
				Nonfatal stroke	Fatal stroke	Total stroke	Angina	Nonfatal MI	Fatal MI	SD	Total CHD	Total macrovascular	Microvascular complications
No orlistat		0.0135	0.0068	0.0016	0.0016	0.0032	0.0059	0.0068	0.0043	0.0008	0.0178	0.0210	0.0067
Clark 1998	10	0.0061	0.0025	0.0012	0.0005	0.0017	-0.0009	0.0026	0.0027	0.0004	0.0049	0.0065	0.0024
Orlistat effect	6	0.0036	0.0015	0.0007	0.0003	0.0010	-0.0005	0.0016	0.0016	0.0003	0.0029	0.0039	0.0015
Orlistat		0.0099	0.0053	0.0009	0.0013	0.0022	0.0064	0.0052	0.0027	0.0005	0.0149	0.0171	0.0052

SD, sudden death; CHD, coronary heart disease; RR, relative reduction. Base risk and end effect with orlistat appears in bold. *Example: all cause mortality (total death): baseline probability = 0.0135 per year. Based on a reduction of 10% HbA_{1c}, the risk reduction would be $0.4 \cdot 0.0135 \cdot 1.125$ (= correction factor) = 0.0061. With orlistat, the effect will be 6/10 of the previous figure = $0.6 \cdot 0.0061 = 0.0036$. The net risk with orlistat = 0.0099.

RESEARCH DESIGN AND METHODS

Epidemiological model

Cost-effectiveness was analyzed using a Markov state transition model (15) and decision analytical software (DATA 3.5) (16). The Markov process technique simulates the evolution of a cohort of patients over time, when therapy is initiated with a specific treatment option. In Markov processes, time progresses in units of fixed length, called stages. At each stage, 6 months in our analysis, a patient is in a given health/treatment state. At each new stage, the patient can move from one state to another. In total, 20 stages (equal to 10 years) were considered. We applied this 10-year horizon because complications related to obesity and diabetes only become apparent after many years and because clinical guidelines in cardiology systematically refer to 10 years as a relevant period for assessing a patient's cardiovascular risk (17).

The model evaluates the two possible scenarios in the considered patient population: orlistat versus no orlistat. All patients enter the model in a health state defined as "obese, type 2 diabetic, and free of complications."

Complications of diabetes can be divided into micro- and macrovascular. Microvascular complications include end-stage renal disease, retinopathy, neuropathy, and foot ulcers. Macrovascular complications include coronary heart disease and ischemic stroke. In the model, every 6 months, diabetic patients have a risk to progress to one of these complication clusters. In other words, patients will be able to stay in the same state of health (without complications), move to another state with complications (micro- or macrovascular or both), or die. It was as-

sumed that patients could not evolve directly to the "micro- and macrovascular complications" state. This is because no clinical data on this transition are available. In other words, we assume that within the same 6 months, a patient can, for example, not have a myocardial infarction (MI) and become blind, which is a conservative assumption.

Population

The target population consists of obese type 2 diabetic patients without micro- or macrovascular complications. At start, four subgroups were defined depending on the presence or absence of hypertension and/or hypercholesterolemia.

Clinical data applied in the model

General considerations. To assess the effect of orlistat, ideally, a regression equation should be applied to predict the independent effect of the change in BMI on the incidence of complications and death (10,11). Unfortunately, for obese diabetic patients, such a regression equation does not exist. Therefore, the effect on mortality and micro- and macrovascular complications of treating patients with orlistat was assessed in two steps: 1) the effect of weight loss with orlistat on risk factors, and 2) the effect of risk factors on morbidity and mortality. It is thereby assumed that improving risk factors leads to a reduction of the number of complications, independently of the way these improvements are achieved (10).

Effects of weight loss with orlistat (first step) on the considered cardiovascular risk factors were published by Hollander et al. (5). In this double-blind placebo-controlled trial, 1 year of orlistat and hypocaloric diet was compared with placebo and hypocaloric diet in 391 obese

type 2 diabetic patients with a mean BMI at study entry of 34.5 kg/m².

For every subgroup, a similar approach was followed, but baseline levels of risk factors and effects of orlistat may obviously differ. This is discussed in the following paragraphs.

Obese type 2 diabetic patients free of events, without hypertension, and without hypercholesterolemia

The baseline data (no orlistat) regarding risk on micro- and macrovascular complications are based on the UKPDS substudy in obese patients treated with metformin (8).

Clark reported that over the range of HbA_{1c} concentrations from 7 to 11%, the relative risk of complications is independently reduced by 40% for every 10% reduction in HbA_{1c} concentration (18). Hollander et al. (5) reported HbA_{1c} levels of 7.50% at the time of randomization in both groups. After the 1-year study period, a decrease of $0.28 \pm 0.09\%$ was observed in the orlistat group compared with an increase of $0.18 \pm 0.11\%$ in the placebo group ($P < 0.001$) (5), i.e., an absolute difference of 0.46% in HbA_{1c} between the two treatment groups or a relative improvement of 6.0% was observed. Thus, if a 10% relative reduction of HbA_{1c} results in a 40% risk reduction in a linear way (18), a 6% relative reduction of HbA_{1c} is estimated to result in a 24% risk reduction on complications. The relation between the risk reductions of different complications obtained with metformin, published in the UKPDS (8), were then applied in order to calculate the relative reduction of each individual complication.

As an example, in Table 1, for this subgroup, the yearly event rate is shown for both treatment options. Because

6-month stages are used, transition probabilities had to be calculated for this time period using the following formula: $\text{Transition}_{6\text{ months}} = 1 - (1 - \text{Transition}_{12\text{ months}})^{6/12}$ (19).

Obese diabetic patients with hypercholesterolemia

In a patient group with LDL cholesterol ≥ 130 mg/dl treated with orlistat, a mean decrease of 17.05 mg/dl (mean base value 150 mg/dl) in LDL cholesterol was observed compared with 2.32 mg/dl in the placebo group (5). In comparison, in the diabetic patients included in the Helsinki Heart Study (HHS) (20), a decrease in LDL cholesterol of 21.9 mg/dl reduced the incidence of MI and cardiac death 68%. Building on recent evidence from Stratton et al. (21) and Adler et al. (22), we assumed that the effects of orlistat on LDL cholesterol were independent of effects on HbA_{1c}. Therefore, the risk reduction due to the effect on cholesterol was added to the risk reduction due to the effect on HbA_{1c}. Patients with diabetes and hypercholesterolemia will have a higher base risk for fatal and nonfatal MI than diabetic patients without hypercholesterolemia. Therefore, the base risk from the HHS, and not the base risk for the general obese diabetic population from the UKPDS, was applied.

Obese diabetic patients with arterial hypertension

In the UKPDS 38 trial, where intensive blood pressure control was studied in hypertensive diabetic patients, a reduction of diastolic blood pressure of 5 mmHg resulted in a significant decrease in complications (23). With orlistat, in hypertensive diabetes, a reduction of 7.29 mmHg was obtained (5). However, this was lower (but not significantly) than the reduction obtained with placebo (13.0 mmHg). Thus, compared with the placebo group, no extra effect of orlistat on blood pressure can be added. Only the impact on HbA_{1c} (0.48% absolute reduction) is accounted for in this population, starting from a base risk typical for this hypertensive subpopulation. In UKPDS 38, however, the general hypertensive diabetes population was described (23), so in order to calculate the base risk for obese hypertensive patients, a correction factor for obesity had to be applied. This correction factor was the ratio of risk for a given event in the conventionally treated

obese UKPDS population (UKPDS 34) and the conventionally treated general UKPDS population (UKPDS 33) (8,24). The correction factors are 1.03 for MI, 1.10 for stroke, 1.09 for all-cause mortality, and 0.81 for microvascular disease.

Obese diabetic patients with both arterial hypertension and hypercholesterolemia

Here, effects of orlistat on cholesterol are combined with the effect of orlistat in the previous subgroup. We calculated the base risk using the values of the hypertensive UKPDS cohort adapted for obesity, and the nonfatal and fatal MI correction factor was added for hypercholesterolemia (risk with hypercholesterolemia [HHS]/risk without hypercholesterolemia [UKPDS 34]) (20,24). The correction factors are 1.99 for nonfatal MI and 1.98 for fatal MI.

Model assumptions

In the Hollander trial (5), an extra 4.2% of patients treated with orlistat were able to stop oral antidiabetes treatment. Because the blood glucose levels of these patients are not known, it is impossible to predict the risk of events for these patients, so, for reasons of conservatism, these patients remained in the diabetes group. Of course, for the calculation of resource use, drug use will be calculated for this small patient group (discussed further in detail).

According to European registration, orlistat can only be administered for 2 years. Thus, for the model, a 2-year administration of orlistat was assumed. It has been reported that 5 years after a weight reduction program is stopped, almost all weight is regained (6). If all weight is regained, risk on complications will be the same as in the not-treated group. Hence, in the model, risk for complications and mortality returns to placebo values in function of weight catch-up over the 5 years after discontinuation of orlistat. As a result, 7 years after study start, the placebo value is reached.

Costs

The perspective taken is that of the health care consumer. The cost of micro- and macrovascular complications in Belgium was studied in the Cost of Diabetes in Europe-Type 2 (CODE-2) study (25). The total health care cost was 1,726 Euro, 2,578 Euro, 3,844 Euro, and 5,443 Euro for 1 year for patients without complica-

tions, with microvascular complications, with macrovascular complications, and with both micro- and macrovascular complications, respectively. These costs were reported for the year 1998 and were adapted to year 2000 values using a 3% inflation rate. In the analysis, future costs have been discounted at 3%. There is no clear consensus in Europe with regard to the discounting of life years (LY). In our model, we applied a 0% discount rate for LY in the base case calculation and varied this figure in sensitivity analyses.

The drug cost for orlistat per patient per year from the public insurance perspective would be 881 Euro. Metformin, the base treatment for obese diabetic patients, costs 119 Euro per patient per year. As mentioned before, in the trial of Hollander et al. (5), an extra 4.2% of patients could stop taking oral antidiabetics, whereas an extra 10.1% had an average reduction in medication intake of 24.8%.

RESULTS

Base case

The results for the different subgroups are shown in Table 2. In obese type 2 diabetic patients without arterial hypertension (AHT) and without hypercholesterolemia, 0.08 LY can be gained over the study period. The incremental cost-effectiveness was 19,986 Euro per LY gained, i.e., approximately what is generally accepted as good value for money (26). The estimated mortality rate over the 10-year study period was 11.7% in the orlistat group compared with 12.7% in the control group. In other words, for every 100 patients treated with orlistat, one life can be saved.

In patients with hypercholesterolemia, 0.204 LY can be gained, resulting in a cost-effectiveness of 7,407 Euro/LYG.

The best results are obtained in diabetic patients with AHT and hypercholesterolemia. Here, a cost per LYG of 3,462 Euro has been found.

Sensitivity analysis

Different sensitivity analyses were applied in the different subgroups. Only the results in the group without AHT or hypercholesterolemia and the group with both AHT and hypercholesterolemia are shown, except for the effect of orlistat on cholesterol, where the two analyses in the hypercholesterolemic patients are shown (Table 3).

Table 2—Cost-effectiveness in obese diabetes free of events

Patient group	Strategy	Cost (Euro)	Incremental cost	Effect	LYG	Cost-effectiveness	Cost/LYG
Free of events	Placebo	15,573		9.381		1,660	
	Orlistat	17,180	1,608	9.462	0.08	1,816	19,986
Hypercholesterolemia	Placebo	15,741		9.197		1,712	
	Orlistat	17,255	1,514	9.401	0.204	1,835	7,407
AHT	Baseline	15,450		8.703		1,775	
	Orlistat	17,128	1,678	8.93	0.227	1,918	7,388
Hypercholesterolemia + AHT	Baseline	15,444		8.266		1,868	
	Orlistat	17,085	1,641	8.74	0.474	1,955	3,462

The effects of a 3% discount per year would increase cost per LYG from 19,986 to 23,522 Euro for obese diabetic patients without other risk factors and from 3,462 to 4,062 Euro for patients with AHT and hypercholesterolemia.

Reducing and increasing effectiveness of orlistat will alter risk for an event (death and micro- and macrovascular complications). Hollander observed a $0.46 \pm 0.14\%$ difference in HbA_{1c} between the two treatment groups. This is a relative difference of $6.0 \pm 1.8\%$. A sensitivity analysis was performed using this standard deviation as interval. Thus, the decrease of risk on complications ranges between 16.7 and 31.3%. The resulting incremental cost-effectiveness ranges between 28,164 and 14,751 Euro/LYG for patients without other cardiovascular risk factors (Table 3).

If the risk reduction due to the effect on LDL cholesterol is only 50% of the value applied in the base case, incremental cost-effectiveness does not change significantly.

Finally, in the base case, we assumed that catch-up of weight and thus evolution to risk of the no weight loss group takes 5 years. If this catch-up period was only 2.5 years, incremental cost-effectiveness ratios would increase but remain very good for patients with AHT and hypercholesterolemia (Table 3).

CONCLUSIONS— The objective of this study was to predict long-term health and economic outcomes of orlistat in obese type 2 diabetic patients.

Therefore, we examined the impact of weight loss due to orlistat on different cardiovascular risk factors and extrapolated this impact to morbidity and mortality outcomes based on results of long-term trials in diabetic patients.

A 40% risk reduction obtained for every 10% relative reduction in HbA_{1c} was observed in patients with type 1 diabetes (18) and extrapolated to type 2 diabetes by other authors (10,11,18,27). This risk reduction was confirmed for type 2 diabetes by a more recent publication of the UKPDS investigators (21).

A debatable aspect of our analysis is that for patients with hypercholesterolemia, we independently added the beneficial effects on HbA_{1c} associated with weight loss caused by orlistat to the effects on LDL cholesterol. This may be an overestimation of the effects of orlistat. However, besides the evidence from Stratton et al. (21) and Adler et al. (22), a study on 290 diabetic patients with obesity and hypercholesterolemia showed that the effect of orlistat on cholesterol is independent of weight loss (28).

We applied results of the HHS to cal-

culate risk reduction obtained with orlistat. Although both the HHS and the Hollander trial were in type 2 diabetic patients, there were some differences in the baseline characteristics (20). Mean BMI was higher in the Hollander trial (34.5 vs. 28.5 kg/m²), but mean LDL cholesterol level was lower (150 vs. 200 mg/dl). A higher baseline value facilitates the absolute decrease in LDL cholesterol. Hence, applying HHS data is disadvantageous for orlistat, and is thus a conservative approach.

The comparison in our evaluation was performed versus the placebo group of Hollander et al. Because both groups received the same lifestyle modifications (hypocaloric diet), improvements in cardiovascular risk factors were due to orlistat. In real practice, the improvements versus baseline may be weaker because of poor compliance with diets (29). The im-

Table 3—Sensitivity analysis

	Incremental cost (Euro)	Incremental effect (LYG)	Cost-effectiveness (Euro/LYG)
Discounting effects 3%			
Free of events	1,608	0.070	23,522
With AHT and hypercholesterolemia	1,641	0.400	4,062
Effect of orlistat on HbA _{1c}			
Free of events			
– Standard deviation	1,622	0.058	28,164
+ Standard deviation	1,601	0.109	14,751
With AHT and hypercholesterolemia			
– Standard deviation	1,684	0.428	3,930
+ Standard deviation	1,595	0.522	3,055
Effect of orlistat on LDL cholesterol			
Hypercholesterolemia	1,681	0.388	4,339
With AHT and hypercholesterolemia	1,569	0.164	9,596
Catch up period: 2.5 years			
Free of events	1,619	0.061	26,527
With AHT and hypercholesterolemia	1,631	0.357	4,565

provement of the active drug versus the comparator may be stronger in real life because the comparison is then between orlistat and “no drug for treating obesity” and not between orlistat and placebo.

Another element is that decreasing cholesterol will also decrease the number of strokes and retinopathy (microvascular disease). This is not taken into account because the HHS did not provide those data (20,30,31). Also, the study did not examine potential noncoronary effects of weight loss, such as the effect on cancer and certain musculo-skeletal disorders, e.g., knee osteoarthritis, and lower back pain.

Subgroup analyses were conducted related to hypertension and hypercholesterolemia. Unfortunately, no data were available to draw conclusions based on different baseline BMI levels in this population. Not only is the effect of BMI in diabetic patients poorly studied, but age also seems to be a factor that influences the impact of BMI, which would further complicate such an analysis (32).

It should finally be noted that the costs of treatment may vary widely from country to country, and thus the results shown here may not be directly applicable to other countries. On the other hand, Belgium is associated with rather low costs of complications compared with other countries, hence our results may again be conservative (33).

Incremental cost-effectiveness of orlistat for 2 years in patients with diabetes and obesity, free of events, and without hypertension or hypercholesterolemia is estimated at 19,986 Euro/LYG. This is approximately what is considered cost-effective (26), but sensitivity analysis showed that the conclusion of cost-effectiveness lacks robustness for these patients. Treating only obese diabetic patients with hypercholesterolemia or hypertension, and especially those with combined hypertension and hypercholesterolemia, widely falls within the range of what is generally accepted as good value for money. Sensitivity analyses prove the robustness of these results.

In conclusion, our results suggest that orlistat is cost-effective in the management of obese diabetic patients, especially with presence of hypercholesterolemia and/or hypertension. As with all new drugs, exercises such as this are important for timely assessment of the potential cost-effectiveness. Observational evi-

dence on longer-term benefits of orlistat (>2 years) would be of importance for future decision-making and validation of our results.

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