The role of orlistat in the treatment of obese patients with mild to moderate hypercholesterolaemia: consequences for coronary risk

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Abstract

This study investigated the effect of orlistat on weight loss and serum lipid parameters in obese patients with hypercholesterolaemia. A total of 215 adult obese patients (body mass index ≥30 kg/m^2) with hypercholesterolaemia (total plasma cholesterol ≥6.5 mmol/L or plasma low density lipoprotein cholesterol ≥4.2 mmol/L) were recruited for screening at 12 out-patient clinics in the UK. Of these, 142 patients were randomised to receive double-blind treatment for 24 weeks with orlistat 120 mg (n=71) or placebo (n=71) three times daily in combination with a mildly hypocaloric diet. Patients completing the double-blind phase (orlistat n=42, placebo n=55) were eligible to enter a further 28-week open-label phase and received orlistat 120 mg three times daily in combination with the hypocaloric diet.

Mean weight loss after 24 weeks was 4.4 kg (4.4%) in the orlistat group *vs.* 2.6 kg (2.5%) with placebo (p<0.01). At the end of the double-blind phase, 44.0% of orlistat-treated patients *vs.* 18.0% of placebo recipients had lost ≥5% of their initial body weight (p<0.001), and 7.6% *vs.* 4.2% had lost ≥10% (p=NS). Patients who continued on orlistat during the open-label phase had a mean weight loss of 4.97 kg (4.86%) after 52 weeks. Patients who switched to orlistat had a mean weight loss of 4.28 kg (4.23%). Orlistat was associated with significantly greater reductions than placebo in plasma total cholesterol (-10.88 ± 1.36% *vs.* -3.25 ± 1.33%; p<0.001) and LDL-cholesterol (-14.14 ± 2.68% *vs.* -3.68 ± 3.61%; p<0.05) during the double-blind phase. Despite similar weight loss at the end of the 52-week period, patients who remained on orlistat throughout the study had greater improvements in plasma lipid concentrations than patients who switched to orlistat after 24 weeks.

Orlistat, in combination with a mildly hypocaloric diet, promotes clinically meaningful weight loss and improvements in lipid concentrations in obese patients with hypercholesterolaemia.

Key words: obesity, hypercholesterolaemia, cardiovascular risk, orlistat.

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Introduction

Obesity is a chronic, progressive, relapsing, metabolic disease associated with high morbidity and early mortality.[1] Obesity is commonly associated with type 2 diabetes, hypertension and dyslipidaemia and all of these factors, including obesity itself, have been identified as independent risk factors for coronary heart disease.[2]

The prevalence of clinical obesity has doubled in the UK between 1980 and 1991, and continues to rise.[3,4] This is primar-

ily due to lifestyle changes, notably higher levels of dietary fat intake and lower levels of physical activity. The energy intake from dietary fat in households has not been increasing since the mid 1980s, but this period has coincided with an enormous expansion in eating outside the home and fast food, predominately high in dietary fat. The Scottish Intercollegiate Guidelines Network has reported that 14% of adult males and 17% of adult females are obese.[5] The 1997 National Health Survey for England reports a similar situation, with 17% of men and 20% of women being defined as obese.[6]

Modest weight loss (5–10% of initial body weight) is associated with significant improvements in obesity-related co-morbidities.[7,8] Although diet and exercise are recommended means of losing weight, they are generally ineffective in maintaining weight loss long term. Adding drug therapy to a regimen of caloric restriction may facilitate weight loss and more importantly prevent weight regain in the longer term.

Orlistat is a non-systemically acting anti-obesity agent that inhibits lipase activity in the gastrointestinal tract, thereby reducing the absorption of ingested dietary fat.[9] Pharmacological studies have shown that orlistat used three times daily with each main meal exerts its optimal effect, an approximately 30% reduction in the absorption of dietary fat, at a dose of 120 mg three times per day (tid).[10] Orlistat, in combination with a mildly hypocaloric diet (600 kcal/day energy deficit with 30% of calories as fat), promoted clinically significant weight loss in obese patients.[11-13] Furthermore, orlistat partially prevented weight regain during a second year of treatment[11,13] and prevented weight regain following six months of conventional dieting.[14] The National Institute for Clinical Excellence (NICE) has recently produced prescribing guidelines for the use of orlistat in the treatment of obesity in adults.[15]

Plasma lipid profile is one of the considerations when assessing cardiovascular risk in obese patients.[16,17] Elevated total cholesterol concentrations increase the risk of developing coronary heart disease.[18,19] In particular, increased low-density lipoprotein cholesterol (LDL-C) concentrations are associated with a substantial increase in coronary risk. Low serum high-density lipoprotein cholesterol (HDL-C) and high serum triglyceride concentrations are also significant risk factors for cardiovascular disease, this profile being particularly atherogenic by altering the nature of the LDL particle.[20,21] Clinical studies with orlistat have shown that weight loss is associated with significant improvements in lipid profiles in obese patients with or without type 2 diabetes.[11-13] The potential effect of orlistat as a lipid-lowering agent may have been underestimated in these studies as less than half of the patients involved had raised LDL or total cholesterol levels.

The objective of this study was to investigate the effect of orlistat on body weight and plasma lipid parameters in obese patients with hypercholesterolaemia.

Methods

Patients

Patients were recruited from 12 out-patient clinics in the UK specialising in obesity and/or dyslipidaemia. Ethics Committee approval was obtained from all participating centres prior to recruitment and patients gave their informed consent. The study was conducted in accordance with Good Clinical Practice. Obese (body mass index ≥30 kg/m^2) male or female patients, aged ≥18 years, with total plasma cholesterol ≥6.5 mmol/L or LDL-C ≥4.2 mmol/L, were eligible for entry into the study. Women of child-bearing potential were included if they were using adequate contraception. Patients were excluded if they had experienced myocardial infarction or major surgery within three months prior to screening, had active gastrointestinal or pancreatic disease, type 1 diabetes, uncontrolled hypertension, histories of carcinoma, gastrointestinal surgery for weight loss, post-surgical lesions, bulimia or laxative abuse, drug or alcohol abuse. Patients were also excluded if they were undergoing treatment with any of the following medications: drugs altering appetite or lipid concentrations, fish oil supplements, retinoids, systemic steroids (other than sex hormone replacements) or anticoagulants.

Study design

Of the 215 patients who were screened, 142 were eligible to be randomised to double-blind treatment with orlistat 120 mg or placebo tid with main meals for 24 weeks. All randomised patients were advised to follow a hypocaloric diet containing 30% of calories as fat and a maximum of 300 mg/day cholesterol. Total energy expenditure was calculated by multiplying the patient's basal metabolic rate as estimated from body weight by 1.3; from this value, 600 kcal/day was subtracted. The hypocaloric diet was achieved by a mild reduction in food intake from each of the five major food groups, with dietary advice being provided by a state-registered dietitian. Patients also received advice on physical activity.

Patients who completed the double-blind phase entered a 28-week open-label phase and received orlistat 120 mg tid in combination with the mildly hypocaloric diet. All patients entering the open-label phase saw a dietitian to reinforce the hypocaloric diet containing 30% of calories as fat and a maximum of 300 mg/day cholesterol. Study design is shown in figure 1.

Patients attended the clinic for assessments at a screening visit (up to four weeks prior to randomisation), at baseline (week 0) and every four weeks up to week 24 during the double-blind phase. During the open-label phase (week 24–52) patients attended the clinic at weeks 30, 36, 44 and 52.

Efficacy assessments

The primary efficacy measure in the double-blind phase of the study was weight loss. Secondary efficacy parameters were plasma lipid concentrations (total cholesterol, LDL-C, HDL-C, VLDL-C and triglycerides), fasting plasma glucose, blood pressure and waist:hip ratio. Body weight, waist and hip circumferences and resting supine blood pressure were measured at all visits. Fractionated plasma lipid concentrations and fasting plasma glucose were measured at screening and weeks 0 (not glucose), 4, 12, 24, 36 and 52.

Figure 1. Study design

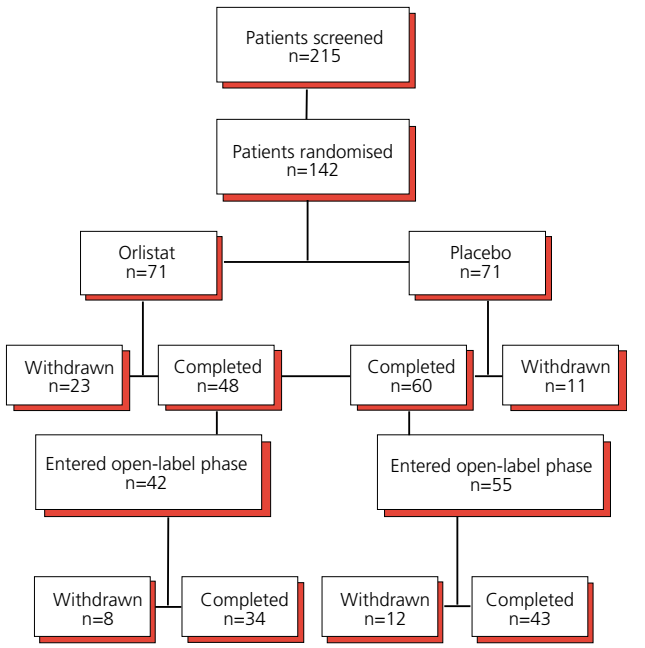


Table 1. Characteristics of the intent-to-treat population at randomisation

Characteristic	Orlistat (n=66)	Placebo (n=71)
Sex (male/female)	28/38	26/45
Age (years)	52.1 ± 9.2 (31–76)	51.0 ± 10.5 (30–71)
Weight (kg)	100.6 ± 18.1 (71.0–166.0)	101.4 ± 20.2 (68.4–175.1)
Height (cm)	165.8 ± 9.6 (151.0–186.0)	165.1 ± 9.0 (147.0–186.0)
Body mass index (kg/m^2)	36.5 ± 5.48 (29.6–54.5)	37.1 ± 6.27 (29.6–59.3)
Systolic blood pressure (mmHg)	136.9 ± 14.8 (110–170)	140.0 ± 16.4 (108–180)
Diastolic blood pressure (mmHg)	82.6 ± 8.3 (70–102)	84.0 ± 9.1 (66–115)
Fasting glucose (mmol/L)*	6.8 ± 3.2 (4.1–18.6)	6.3 ± 2.4 (4.2–14.8)
Diagnosed type 2 diabetes (%)	30.3%	19.8%

Key: *measured at screening; data are means ± SD, where appropriate

Tolerability assessments

Vital signs were measured at all visits. Laboratory assessments were performed at screening, week 24 and week 52, and included measurements of whole blood haemoglobin, leucocyte and platelet counts, urea and electrolytes and liver function tests. Adverse events were monitored throughout the study and potential relationship to treatment judged by the investigator. Patients were specifically questioned by body system at each clinic visit. To ensure consistent reporting of gastrointestinal adverse events across study centres, a concise dictionary of preferred terms was employed (as listed later in table 4).

Statistical analysis

The expected standard deviation of mean weight loss after 24 weeks of a calorie-restricted diet plus placebo was approximately 4.0 kg. In the double-blind phase, 37 patients per treatment group would be required to detect a difference of 3.0 kg with a power of 80% at the 5% significance level. Since the expected standard deviation of weight loss in hypercholesterolaemic patients was not available, the planned sample size was 150 patients (allowing for a 25–30% drop-out rate).

An intent-to-treat (ITT) analysis was performed on those patients who had received at least one dose of study medication and had at least one follow-up visit. An analysis of the completers' population (patients who completed 52 weeks of treatment) was also performed. Missing values were replaced using the last-observation-carried-forward method.

The null hypothesis of no significant difference in mean weight loss between placebo and orlistat treatments was tested using an analysis of variance model (ANOVA). The 95% confidence interval of treatment difference based on the least squares mean was also determined. ANOVA was also used to compare differences between treatment groups in changes in lipid parameters. Descriptive analyses only were performed on blood pressure, fasting glucose and waist:hip ratio. For the open-label phase the statistical analysis performed was of an exploratory nature only. All descriptive summaries and all statistical analyses were obtained using SAS-PC version 6.12 (SAS Institute, Cary, NC, USA). Statistical tests were carried out at the 5% level of significance.

Results

Patient demographics

Double-blind phase

A total of 142 patients were randomised to double-blind treatment with orlistat (n=71) or placebo (n=71). Five patients randomised to orlistat either did not receive any study medication or failed to return for a follow-up visit and so were not eligible for the ITT analysis. Thus, the ITT population comprised of 66 patients in the orlistat group and 71 patients in the placebo group. Patient characteristics of the ITT population at randomisation were similar in the two treatment groups (table 1). Forty-eight (67%) patients randomised to orlistat and 60 (84.5%) patients randomised to placebo completed the double-blind phase. The main reasons for premature withdrawal in both study groups were adverse events (orlistat, n=11; placebo, n=5), failure to return (n=6;4) and administrative or protocol violation (n=5;3).

Single-blind phase

A total of 42 (29.6%) patients previously randomised to orlistat

Figure 2. Mean (± SEM) weight loss (kg) in patients undergoing treatment with orlistat 120 mg or placebo tid for 24 weeks; 4.40 ± 0.51 kg (range -8.2, 14.3) *vs.* 2.60 ± 0.46 kg (-3.2, 18.6), respectively; *p=0.0091 (ITT population)

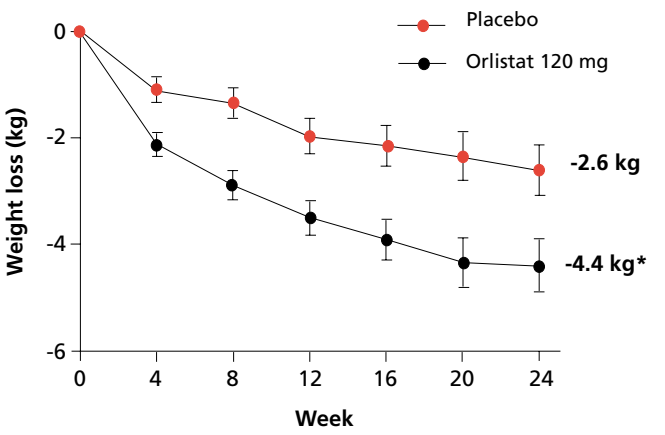
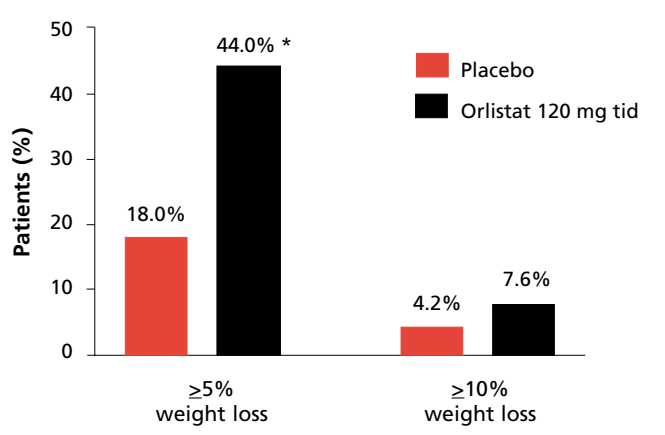


Figure 3. Proportion of patients achieving clinically meaningful weight loss of ≥5% or ≥10% following 24 weeks of double-blind treatment with orlistat 120 mg tid or placebo (*p<0.001) (ITT population)



and 55 (38.7%) patients previously randomised to placebo entered the open-label phase. All patients were re-evaluated with respect to cardiovascular risk and the potential benefits versus risks of continued participation prior to being invited to participate. Eleven patients who completed the double-blind phase were regarded as screening failures and did not enter the open-label phase, seven because they did not want to continue in the study and four because they required additional lipid-lowering treatment. Seventy-seven patients completed the open-label phase (previously on orlistat, n=34; previously on placebo, n=43). Adverse events (orlistat, n=5; placebo, n=5), failure to return (1;1) and protocol violation (0;4) were the main reasons for withdrawal.

Efficacy

Effect on body weight

After 24 weeks of double-blind treatment, mean (±SD) body weight had decreased from 100.6 ± 18.1 kg (range 71.0, 166.0) to 96.2 ± 18.0 kg (67.3, 155.5) in the orlistat group and from 101.4 ± 20.2 kg (68.4, 177.1) to 98.8 ± 19.5 kg (67.8, 168.0) in the placebo group. Mean weight loss was significantly greater with orlistat compared to placebo (4.40 ± 0.51 kg [range -8.2, 14.3] *vs.* 2.60 ± 0.46 kg [-3.2, 18.6]; p=0.0091) (ITT population) (figure 2). When expressed as a percentage, mean weight loss was 4.35 ± 0.46% (range -7.8, 12.4%) and 2.50 ± 0.42% (-3.6, 15.8%) for the orlistat and placebo groups, respectively.

At the end of 24 weeks, 44.0% of orlistat-treated patients *vs.* 18.0% of placebo recipients had lost at least 5% of their initial body weight (p<0.001), and 7.6% *vs.* 4.2% had lost at least 10% (p=NS) (figure 3).

In the open-label phase, patients who continued on orlistat maintained their weight loss for a further 28 weeks. Mean weight loss after 52 weeks of continuous orlistat treatment was 4.97 ± 0.77 kg (range -2.0, 22.8) or 4.89 ± 0.76% (range -2.0, 17.1%) (ITT population). For the completers' population, mean weight loss was 5.41 ± 0.98 kg (-2.0, 22.8) or 5.34 ± 0.92% (-2.0, 17.1%).

Weight loss plateaued at 24 weeks in the placebo group but these patients achieved a further mean weight reduction of 1.37 ± 0.52 kg (range -7.0, 11.8) (1.57 ± 0.21% [range -9.2, 14.2%]) when switched to orlistat in the 28-week open-label phase (ITT population). Total mean weight loss from randomisation in this patient group was 4.28 ± 0.79 kg (range -3.9, 27.6) (4.23 ± 0.71% [range -2.8, 23.4]).

Effect on lipid profile

Changes in plasma lipid concentrations during the double-blind phase are summarised in table 2. Both treatment groups were comparable at baseline with respect to lipid concentrations. Orlistat was associated with significantly greater reductions than placebo in plasma total cholesterol (-10.88 ± 1.36% *vs.* -3.25 ± 1.33%; p<0.001) and LDL-cholesterol (-14.14 ± 2.68% *vs.* -3.68 ± 3.61%; p<0.05) after 24 weeks of double-blind treatment. Total cholesterol concentrations continued to decrease in patients who remained on orlistat throughout the open-label phase, resulting in a mean reduction in total cholesterol after 52 weeks of 0.96 mmol/L (12.62%). Changes at the end of the open-label phase are summarised in table 3. Patients who switched to orlistat during the open-label phase showed substantial reductions in total cholesterol of 0.67 mmol/L (8.59%) after 52 weeks. Similarly, patients who remained on orlistat showed mean reductions in LDL-C of 0.91 mmol/L (19.29%) after 52 weeks of treatment. Patients who switched to orlistat showed a mean reduction in LDL-C of 0.40 mmol/L (9.08%) after 52 weeks. There was a non-significant trend towards a greater improvement in triglyceride concentration in the orlistat group compared to the placebo group after 24 weeks of double-blind treatment.

Table 2. Summary of changes in plasma lipid concentrations (mean ± SEM) during double-blind treatment with orlistat 120 mg or placebo (ITT population)

		Orlistat (n=66)	Placebo (n=71)	p value
Total cholesterol (mmol/L)	Baseline	7.44 ± 0.11	7.42 ± 0.14	
	Week 24	6.63 ± 0.13	7.20 ± 0.13	
	Mean change	-0.83 ± 0.12	-0.27 ± 0.10	p<0.001
	% change	-10.88 ± 1.36	-3.25 ± 1.33	
LDL-C (mmol/L)	Baseline	4.35 ± 0.14	4.57 ± 0.12	
	Week 24	3.65 ± 0.14	4.30 ± 0.13	
	Mean change	-0.71 ± 0.12	-0.31 ± 0.12	p=0.018
	% change	-14.14 ± 2.68	-3.68 ± 3.61	
HDL-C (mmol/L)	Baseline	1.33 ± 0.10	1.35 ± 0.10	
	Week 24	1.15 ± 0.10	1.25 ± 0.04	
	Mean change	-0.19 ± 0.10	-0.11 ± 0.03	p=NS
	% change	-9.55 ± 3.20	-5.55 ± 2.31	
LDL-C/HDL-C ratio	Baseline	3.51 ± 0.14	3.73 ± 0.17	
	Week 24	3.34 ± 0.13	3.59 ± 0.13	
	Mean change	-0.18 ± 0.14	-0.12 ± 0.12	p=NS
	% change	0.13 ± 4.53	3.98 ± 4.24	
Total-C/HDL-C ratio	Baseline	5.72 ± 0.27	5.71 ± 0.26	
	Week 24	5.83 ± 0.26	5.91 ± 0.20	
	Mean change	ND	ND	ND
Triglycerides (mmol/L)	Baseline	4.01 ± 0.33	3.47 ± 0.35	
	Week 24	3.87 ± 0.49	3.00 ± 0.02	
	Mean change	-0.15 ± 0.25	-0.42 ± 0.26	ND
VLDL-C (mmol/L)	Baseline	0.75 ± 0.08	0.76 ± 0.09	
	Week 24	0.95 ± 0.10	0.81 ± 0.07	
	Mean change	0.18 ± 0.10	0.05 ± 0.09	p=NS

Key: HDL-C = high-density lipoprotein cholesterol; ITT = intent-to-treat; LDL-C = low-density lipoprotein cholesterol; ND = not determined; NS = not significant; VLDL-C = very low-density lipoprotein cholesterol

Other cardiovascular risk factors

The two treatment groups were comparable at baseline with respect to supine blood pressure (136.9/86.2 mmHg *vs*. 140.0/84.0 mmHg for orlistat and placebo, respectively). After 24 weeks of double-blind treatment, mean blood pressure was 135.8/80.6 mmHg for the orlistat group and 138.3/83.2 mmHg for the placebo group. At screening, mean fasting glucose was 6.80 and 6.28 mmol/L in the orlistat and placebo groups, respectively. Mean fasting glucose concentrations were similar in both treatment groups after 24 weeks (6.39 and 6.40 mmol/L in the orlistat and placebo groups, respectively). Mean fasting glucose at week 52 was 6.40 mmol/L for patients who continued on orlistat and 6.22 mmol/L for patients who switched to orlistat. Both groups showed reductions in waist circumference.

Safety and tolerability

During the double-blind phase, safety profiles in both orlistat and placebo groups were generally similar. A total of 95.5% of patients in the orlistat group and 85.9% of patients in the placebo group reported at least one adverse event. However, most adverse events were normally mild and self-limiting and, with the exception of certain gastrointestinal (GI) system events, were not considered by the investigators concerned to be likely to be study drug-related. More patients in the orlistat group than the placebo group experienced GI adverse events (86.6% *vs.* 42.3%); the most common GI effects are listed in table 4. The majority of GI events were transient and mild to moderate in intensity. Seven patients (10.4%) in the orlistat group and three patients (4.2%) in the placebo group withdrew prematurely because of GI events.

Four serious adverse events were reported in four patients in the orlistat group; elective cytoscopy and hydrodistension, stroke, sleep disorder and benign fluid-filled breast cyst. Ten serious adverse events were reported in six patients in the placebo group; radiculitis in right elbow, cellulitis (in two patients), limb pain in lower left leg, hiatus hernia, gastric ulcer, oesophageal reflux, anaemia, pregnancy and cholecystectomy.

During the open-label phase, adverse events were reported by 92.9% of patients who remained on orlistat and 96.3% of patients who switched to orlistat. GI events were the most frequent events reported, by 54.8% of patients who remained on orlistat and 75.9% of patients who switched to orlistat (table 4). Ten patients withdrew during the open-label phase because of GI events.

Six serious adverse events were reported in four patients who remained on orlistat (neuropathic toe ulcer, cellulitis, severe facial paralysis diagnosed as Bell's palsy, dermal bleeding and upper limb injury caused by road traffic accident, and suicide attempt). One serious adverse event (abdominal pain) was reported in one patient who switched to orlistat.

Discussion

This randomised, double-blind, placebo-controlled study demonstrated that obese patients with hypercholesterolaemia (total plasma cholesterol ≥6.5 mmol/L or plasma LDL-C ≥4.2 mmol/L) who were treated with orlistat lost significantly more weight after 24 weeks compared with placebo (4.5% *vs*. 2.6%; p<0.01). In addition, more than twice as many orlistat-treated patients achieved clinically meaningful weight loss of ≥5%. Patients who remained on orlistat maintained their weight loss during the open-label phase of the study, resulting in mean weight reduction of 4.9% at 52 weeks. The modest weight loss achieved by placebo-treated patients was enhanced on switching to orlistat. This is comparable to findings of an earlier two-year study of orlistat, in which placebo recipients who switched to orlistat during the second year of the study had similar weight loss after two years to patients who received orlistat for the entire study.[11]

Dyslipidaemic subjects, like patients with type 2 diabetes, will typically have received prior intensive individualised dietary advice aimed at lipid lowering and weight reduction and so further weight loss may be difficult to achieve. This was shown in the present study, in which weight loss was lower than that

Table 3. Changes at the end of the open-label phase (week 52) in lipid parameters and weight (mean ± SD) for patients previously on orlistat 120 mg or previously on placebo (ITT population)

		Previously on orlistat (n=41)	Previously on placebo (n=54)	p value
Weight change from week 0 to week 52	Mean change	-4.97 ± 5.40	-4.28 ± 5.82	
	% change	-4.89 ± 4.89	-4.32 ± 5.21	p=NS
Weight change from week 24 to week 52	Mean change	0.67 ± 4.04	-1.37 ± 3.80	
	% change	0.73 ± 4.07	-1.57 ± 3.98	0.024
Total cholesterol change from week 0 to week 52	Mean change	-0.96 ± 1.04	-0.67 ± 1.04	
	% change	-12.62 ± 13.00	-8.59 ± 14.00	p=NS
Total cholesterol change from week 24 to week 52	Mean change	0.07 ± 0.90	-0.47 ± 0.75	
	% change	1.36 ± 13.79	-6.23 ± 10.19	0.006
LDL-C from week 0 to week 52	Mean change	-0.91 ± 1.00	-0.40 ± 1.05	
	% change	-19.3 ± 21.42	-9.08 ± 24.59	0.025
LDL-C from week 24 to week 52	Mean change	0.07 ± 1.04	-0.16 ± 1.02	
	% change	3.26 ± 30.58	-3.90 ± 25.12	p=NS
HDL-C from week 0 to week 52	Mean change	-0.29 ± 0.45	-0.23 ± 0.29	
	% change	-16.72 ± 21.32	-14.60 ± 15.21	p=NS
HDL-C from week 24 to week 52	Mean change	-0.05 ± 0.26	-0.11 ± 0.24	
	% change	-2.60 ± 18.39	-8.03 ± 16.64	p=NS
LDL-C/HDL-C ratio from week 0 to week 52	Mean change	-0.03 ± 1.32	-0.18 ± 1.07	
	% change	-5.29 ± 51.04	-8.65 ± 37.54	p=NS
LDL-C/HDL-C ratio from week 24 to week 52	Mean change	-0.21 ± 0.79	-0.23 ± 1.11	
	% change	-6.38 ± 28.65	-6.16 ± 27.67	p=NS

Key: HDL-C = high density lipoprotein cholesterol; ITT = intent-to-treat; LDL-C = low-density lipoprotein cholesterol; NS = not significant

reported in other randomised, double-blind, placebo-controlled trials of orlistat. In previous studies, weight loss after one year of treatment with orlistat 120 mg was approximately 9–10% compared to 6% with placebo in patients with simple obesity.[11,13]

A high proportion of patients enrolled in this study had type 2 diabetes (30.3% of patients randomised to orlistat and 19.8% of patients randomised to placebo). It is recognised that diabetic patients are more resistant to weight loss than non-diabetic patients.[22] Weight reduction achieved in the present study is comparable to that in a trial of overweight patients with type 2 diabetes in which weight loss after one year of treatment with orlistat 120 mg was 6.2% compared with 4.3% in the placebo group.[12]

Cardiovascular risk factors

Double-blind treatment with orlistat was associated with signifi-

Table 4. Frequency (% of patients) of gastrointestinal adverse events (incidence ≥5%) during double-blind and open-label phases

	Double-blind		Open-label	
	Placebo (n=71)	Orlistat (n=67)	Placebo/ orlistat (n=54)	Orlistat/ orlistat (n=42)
Overall adverse events	85.9	95.5	96.3	92.9
Gastrointestinal				
Liquid stools	9.9	32.8	22.2	19.0
Increased defecation	11.3	23.9	16.7	2.4
Fatty/oily stool	4.2	22.4	22.2	11.9
Soft stools	9.9	22.4	14.8	7.1
Faecal urgency	0.0	16.4	7.4	9.5
Abdominal pain	5.6	13.4	9.2	2.4
Flatulence	8.5	7.5	1.8	0.0
Oily spotting	0.0	6.0	14.8	2.4
Flatus with discharge	2.8	6.0	5.6	0.0

cant reductions in plasma total cholesterol and LDL-C concentrations after 24 weeks. Concomitant with weight loss, patients who remained on orlistat in the open-label phase showed a sustained decrease in LDL-C. However, despite similar weight loss in both treatment groups at week 52, patients who remained on orlistat throughout the study had greater improvements in total cholesterol and LDL-C concentrations than patients who received orlistat during the open-label phase only. This suggests that orlistat may have a lipid-lowering treatment effect independent of weight loss, as has been reported in previous studies.[11,13] Recent data has suggested that this independent effect may be due to the fact that orlistat inhibits the absorption of dietary cholesterol by 25%.[23]

The effects of orlistat on several cardiovascular risk factors, in particular LDL-C, may have a major impact on coronary risk. In the present study, orlistat was associated with a reduction in LDL-C of approximately 10% after 24 weeks (-14.1% *vs.* -3.7% with placebo). Studies of cholesterol-lowering for the primary prevention of coronary heart disease (CHD) have shown that a fall in LDL-cholesterol of 10% is associated with a reduction in CHD risk of about 20%.[24,25] For example, in the West of Scotland Coronary Prevention Study (WOSCOPS), treatment with pravastatin reduced the relative risk of a major coronary event by 31% among 6,595 men, 95% of whom did not have prior CHD.[26] Similar findings were reported by the Air Force/Texas Coronary Atherosclerosis Study (AFCAPS/TexCAPS), in which the risk of myocardial infarction, unstable angina and sudden cardiac death in 6,605 healthy men and women was reduced by 37% after treatment with lovastatin in combination with a low-fat diet.[27]

Orlistat-induced weight loss was also associated with trends towards mild improvements in other cardiovascular risk factors, including plasma fasting glucose and blood pressure, in the present study. These findings are in accordance with previous studies of orlistat.[11,13] Thus, the benefits of orlistat with regard to reducing coronary risk are multifactorial. Modest improvements in multiple CHD risk factors can effectively reduce CHD risk to a greater extent than aggressive targeting of individual risk factors.[17]

Adverse events

Orlistat was well tolerated and most adverse events were mild and transient. GI events occurred more frequently with orlistat than with placebo, as would be expected from the drug's mode of action, but led to treatment withdrawal in only seven patients during the double-blind phase of the study. During the open-label phase, GI events were less frequent in patients who had previously received orlistat than in patients who had switched to orlistat, suggesting that orlistat-treated patients become more compliant with a low-fat diet over time. This effect was noted in the NICE guidance which mentioned that these GI effects may encourage patients to limit their fat intake.[15]

Key messages

- Orlistat reduces body weight in obese patients with hypercholesterolaemia
- Orlistat promotes improvements in lipid levels in obese patients with hypercholesterolaemia

Summary

In conclusion, orlistat, in combination with a mildly hypocaloric diet, promotes clinically meaningful weight loss and improvements in serum lipid concentrations in obese patients with hypercholesterolaemia. The combined effects of orlistat on weight and lipid concentrations have implications for the reduction in cardiovascular risk in obese patients with hypercholesterolaemia.

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