Ursodeoxycholic acid for the prevention of symptomatic gallstone disease after bariatric surgery (UPGRADE): a multicentre, double-blind, randomised, placebo-controlled superiority trial

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Summary

Background Rapid weight loss is a major risk factor for the formation of cholesterol gallstones. Consequently, patients with morbid obesity undergoing bariatric surgery frequently develop symptomatic gallstone disease. This trial assessed the efficacy of ursodeoxycholic acid versus placebo for the prevention of symptomatic gallstone disease after bariatric surgery.

Methods This multicentre, double-blind, randomised, placebo-controlled superiority trial enrolled patients with an intact gallbladder scheduled for laparoscopic Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy in three hospitals in the Netherlands. Patients were randomly assigned (1:1) by a web-based randomisation module to receive 900 mg ursodeoxycholic acid daily for 6 months or matched placebo. Randomisation was stratified by the presence of asymptomatic gallstones at baseline and type of surgery. Patients, clinicians, and study staff were masked to treatment allocation. The primary endpoint was symptomatic gallstone disease within 24 months, assessed in the modified intention-to-treat population (all randomly assigned eligible patients with any post-randomisation measurement). Prespecified subgroup analyses were done based on the stratification groups. Safety was assessed in all patients who took at least one dose of the study drug. This trial is registered with the Netherlands Trial Register, NL5954.

Findings Between Jan 11, 2017, and Oct 22, 2018, 985 patients were randomly assigned to receive either ursodeoxycholic acid (n=492) or placebo (n=493). 967 patients were included in the modified intention-to-treat population, of whom 959 had data available for primary endpoint assessment. 189 (20%) patients had asymptomatic gallstones at baseline and 78 (8%) received a sleeve gastrectomy. Symptomatic gallstone disease occurred in 31 (6·5%) of 475 patients in the ursodeoxycholic acid group and in 47 (9·7%) of 484 patients in the placebo group (relative risk 0·67, 95% CI 0·43–1·04, p=0·071). Logistic regression showed a significant interaction between ursodeoxycholic acid and the presence of asymptomatic gallstones at baseline (p=0·046), with an effect of ursodeoxycholic acid in patients without (0·47, 0·27–0·84, p=0·0081), and no effect in patients with asymptomatic gallstones at baseline (1·22, 0·61–2·47, p=0·57). The effect was stronger in patients without gallstones at baseline undergoing RYGB (0·37, 0·20–0·71, p=0·0016), whereas the subgroup of patients undergoing sleeve gastrectomy was too small to draw clear conclusions. Adverse events were rare. In the ursodeoxycholic acid group, diarrhoea occurred in four (0·9%) of 444 patients and skin rash in two (0·5%) patients. In the placebo group, diarrhoea occurred in two (0·4%) of 453 patients and skin rash in two (0·4%) patients. The total number of serious adverse events did not significantly differ between the trial groups (75 [17%] in 444 patients in the ursodeoxycholic acid group and 102 [23%] in 453 patients in the placebo group). The most common serious adverse events were abdominal pain and internal hernia. No serious adverse event was attributed to the study drug.

Interpretation Ursodeoxycholic acid prophylaxis did not significantly reduce the occurrence of symptomatic gallstone disease in all patients after bariatric surgery. In patients without gallstones before RYGB surgery, ursodeoxycholic acid treatment reduced the occurrence of symptomatic gallstone disease compared with placebo. Further research is needed to assess the efficacy of ursodeoxycholic acid after sleeve gastrectomy.

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Research in context

Evidence before this study

Rapid weight loss is a major risk factor for the formation of cholesterol gallstones. Consequently, patients with morbid obesity undergoing bariatric surgery frequently develop symptomatic gallstone disease. An opportunity to medically prevent symptomatic gallstone disease during rapid weight loss is the administration of ursodeoxycholic acid, an oral bile acid. Before initiation of this trial, we searched PubMed, Embase, and the Cochrane Library for clinical studies published from inception to March 1, 2016, with the search terms "bariatric surgery" and "ursodeoxycholic acid" and "gallstones". No language restrictions were applied. Two meta-analyses and six randomised controlled trials (of which five were included in both meta-analyses) were found. Findings from this systematic review suggested that ursodeoxycholic acid leads to a lower rate of gallstone formation after bariatric surgery (pooled relative risk 0·39, 95% CI 0·21–0·72). However, in all trials the primary endpoint was gallstone formation, which is not a clinically relevant endpoint since many patients remain asymptomatic. Apart from the absence of a clinically relevant primary endpoint, the trials excluded patients with asymptomatic gallstones before bariatric surgery. Additionally, most trials were underpowered and showed a high loss of follow-up. Finally, three trials included outdated types of bariatric surgery, such as vertical banded gastroplasty and adjustable gastric banding, which lead to less weight loss in comparison with Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy. A placebo-controlled randomised trial was thus warranted to assess the efficacy of ursodeoxycholic acid in preventing symptomatic gallstone disease among patients undergoing bariatric surgery.

Added value of this study

We found a beneficial effect of ursodeoxycholic acid in patients undergoing RYGB who did not have gallstones at baseline, but in patients with asymptomatic gallstones at baseline there was no effect. Ursodeoxycholic acid prophylaxis for 6 months was found to reduce the formation of gallstones, occurrence of symptomatic gallstone disease, and performance of cholecystectomy in patients without gallstones before bariatric surgery. No beneficial effect was observed in patients with asymptomatic gallstones before surgery, and the subgroup of patients who underwent a sleeve gastrectomy was too small to draw clear conclusions.

Implications of all the available evidence

We provide evidence from a multicentre, double-blind, randomised, placebo-controlled trial that ursodeoxycholic acid prophylaxis should be given to patients without gallstones before RYGB surgery. Further research is needed to assess the efficacy of ursodeoxycholic acid prophylaxis after sleeve gastrectomy.

Introduction

The escalating epidemic of obesity has become a major global health-care issue.[1] According to WHO, more than 1·9 billion adults (39% of those aged >18 years) were overweight in 2016, and over 650 million (13%) were obese.[2] Bariatric surgery is safe and the only treatment that achieves long-term weight loss and reduction of obesity-related diseases.[3] In 2016, the estimated number of bariatric interventions done worldwide was around 635 000.[4]

Obesity and rapid weight loss are both well known risk factors for the formation of cholesterol gallstones.[5] Of the patients who undergo bariatric surgery, up to 40% develop gallstones,[6–8] and approximately 8–15% become symptomatic and require a cholecystectomy.[9–11] Additionally, in case of biliary pancreatitis, cholangitis, or choledocholithiasis, conventional endoscopic retrograde cholangiopancreatography cannot be done after laparoscopic Roux-en-Y gastric bypass (RYGB) due to the altered anatomy. Consequently, more invasive procedures are necessary.

Although international variation in clinical practice does exist, concomitant cholecystectomy at the time of bariatric surgery is in general reserved for patients with symptomatic gallstone disease before bariatric surgery.[12,13] An opportunity to medically prevent symptomatic gallstone disease during rapid weight loss is the administration of ursodeoxycholic acid, an oral bile acid. Ursodeoxycholic acid is known to induce unsaturated gallbladder bile that hampers the nucleation of cholesterol crystals. There is robust evidence that ursodeoxycholic acid reduces the formation of cholesterol gallstones during rapid weight loss induced by very low-calorie diets or bariatric surgery.[6,14,15] However, gallstone formation is not a clinically relevant outcome because many patients remain asymptomatic. There is currently no high-level evidence that ursodeoxycholic acid prophylaxis is also associated with a reduction of symptomatic gallstone disease. Hence, ursodeoxycholic acid is not routinely prescribed in most countries. Additionally, previous trials excluded patients with asymptomatic gallstones before surgery, whereas in current practice, no preoperative gallbladder screening is done in general unless patients are symptomatic.[13] Moreover, in patients with asymptomatic gallstones before surgery, ursodeoxycholic acid might also reduce the occurrence of symptomatic gallstone disease by additionally decreasing the risk of already present gallstones to become symptomatic.[16]

To address the decisional uncertainty of whether ursodeoxycholic acid should be prescribed, we did a multicentre, randomised controlled trial to assess the efficacy of ursodeoxycholic acid in preventing symptomatic gallstone disease among patients undergoing bariatric surgery.

Methods

Study design and participants

The Ursodeoxycholic Acid for the Prevention of Symptomatic Gallstone Disease after Bariatric Surgery (UPGRADE) trial was a multicentre, double-blind, randomised, placebo-controlled superiority trial done in three hospitals in the Netherlands (appendix p 3). The trial was done according to the previously published trial protocol and statistical analysis plan.[17,18] In the Netherlands, patients aged 18–65 years with a body-mass index (BMI) of 40 kg/m² or above, or with a BMI of 35–40 kg/m² in combination with one or more obesity-related diseases, are considered eligible for bariatric surgery. The initial study design included participants with an intact gallbladder scheduled for laparoscopic RYGB but was soon (July 4, 2017) amended to allow the inclusion of individuals scheduled for laparoscopic sleeve gastrectomy. The exclusion criteria were: the presence of symptomatic gallstone disease before bariatric surgery; previous bariatric surgery; previous gallbladder surgery; ascertained or presumptive hypersensitivity to ursodeoxycholic acid; inflammatory bowel disease and other conditions of the small intestine and liver that might interfere with the enterohepatic circulation of bile salts; and intake of ursodeoxycholic acid within the last 30 days before screening. The UPGRADE trial was done in accordance with the Declaration of Helsinki and the Dutch Law for Research Involving Human Subjects. The ethical committee of the Slotervaart Hospital and Reade (Amsterdam, Netherlands) and the boards of directors at each hospital approved the trial protocol before local conduct started. All participants gave written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1) to receive 900 mg ursodeoxycholic acid daily for 6 months or placebo. Randomisation was done before surgery by central study coordinators using a web-based randomisation module with randomly varying block sizes (4, 6, and 8), and stratified by the presence of asymptomatic gallstones at baseline (present or not) and the type of scheduled surgery (RYGB or sleeve gastrectomy). Placebo tablets were identical in appearance to ursodeoxycholic acid tablets and each package was given a randomisation number to ensure masking of patients, clinicians, and study staff. All were masked until the last patient completed 24 months of follow-up and the primary endpoint adjudication was done.

Procedures

Study staff informed patients about the trial during the screening for bariatric surgery. If eligible for surgery, patients were asked to participate, and informed consent was obtained. Gallbladder ultrasonography was done before randomisation. To prevent a nocebo effect, the result of the ultrasonography was not mentioned to the patient nor in the patient record. Patients assigned to ursodeoxycholic acid were given two tablets of 450 mg of ursodeoxycholic acid daily for 6 months and patients assigned to placebo were given matched placebo tablets. We chose to treat patients according to a fixed dose regimen of ursodeoxycholic acid of 900 mg per day (7–8 mg/kg for most patients at baseline). The day after surgery, patients received the study drug and were instructed to start it as soon as possible, preferably within 2 weeks, but within 8 weeks at the latest. A maximum mid-term break of 4 weeks was allowed during the treatment course. Patients with a protocol violation concerning eligibility did not receive the allocated treatment and were removed from the trial (appendix p 3). Follow-up visits occurred at 6 weeks and 16 weeks, and at 6, 12, and 24 months after surgery. Patients were asked to return the study drug packing to assess compliance. We administered the EuroQol 5 Dimensions (EQ-5D-5L) questionnaire[19] at baseline, and at 3, 6, 12, 18, and 24 months. The RAND 36-Item Health Survey (RAND-36)[20,21] was gathered during

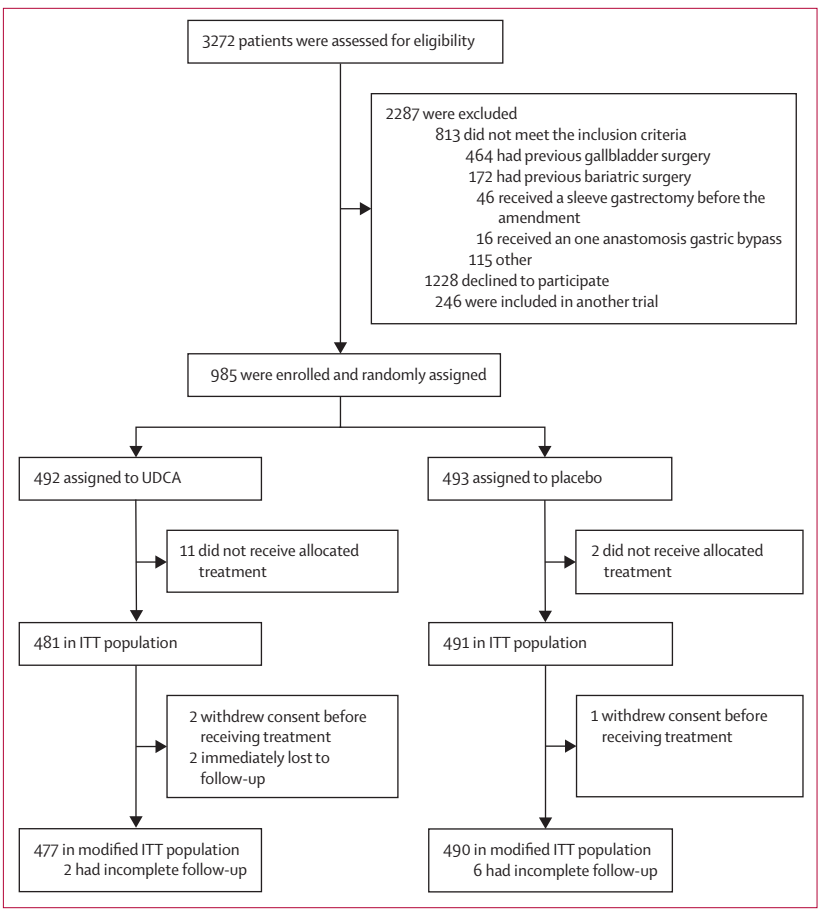

Figure 1: **Trial profile**
13 patients who were randomly assigned did not receive the allocated treatment because eligibility was violated (eight patients received a sleeve gastrectomy before the amendment was approved, in three patients the surgery was not feasible due to adhesions, and two patients did not undergo surgery during the trial period). Patients with incomplete follow-up were excluded from the primary endpoint analysis. ITT=intention-to-treat. UDCA=ursodeoxycholic acid.

See **Online** for appendix

	UDCA group (n=477)	Placebo group (n=490)
Age, years	45·5 (11·2)	44·7 (11·0)
Sex		
Female	381 (80%)	391 (80%)
Male	96 (20%)	99 (20%)
Weight at baseline, kg	116·1 (18·8)	115·8 (17·1)
Body-mass index at baseline, kg/m²	40·1 (4·8)	40·2 (4·7)
Comorbidities at baseline		
Hypertension	227 (48%)	247 (50%)
Dyslipidaemia	142 (30%)	162 (33%)
Type 2 diabetes	64 (13%)	94 (19%)
Statin use at baseline	77 (16%)	90 (18%)
Asymptomatic gallstones at baseline	94 (20%)	95 (19%)
Type of surgery		
Roux-en-Y gastric bypass	439 (92%)	450 (92%)
Sleeve gastrectomy	38 (8%)	40 (8%)
Health utility score*	0·83 (0·19)	0·85 (0·16)

Data are mean (SD) or n (%). The appendix (pp 8–10) describes additional baseline characteristics, the baseline characteristics of the excluded patients who were randomly assigned, and baseline characteristics of the intention-to-treat population. UDCA=ursodeoxycholic acid. *Health utility scores are based on the scoring profiles of the EQ-5D-5L questionnaire. Observed health utility scores range from –0·08 (health state worse than death) to 1 (perfect health state).

Table 1: **Baseline characteristics of the modified intention-to-treat population**

regular care visits (independent of participation in the trial), which took place at baseline and at 12 and 24 months. Gallbladder ultrasonography was repeated at 24 months (window 18–30 months). Data were collected by study coordinators using a standardised case report form. An independent monitor, masked to treatment allocation, assessed the study documents, and compared them with the source documents.

Outcomes

The primary endpoint was the proportion of patients with symptomatic gallstone disease within 24 months of follow-up. Symptomatic gallstone disease was defined as biliary disease (biliary pancreatitis, acute cholecystitis, choledocholithiasis, cholangitis, or biliary colic), for which a hospital visit or admission was required (see trial protocol for detailed definitions of biliary disease).[17] Secondary endpoints consisted of the presence of gallstones or sludge on postoperative ultrasonography, the number of cholecystectomies within 24 months, time to symptomatic gallstone disease and cholecystectomy, therapy compliance, quality of life, health utility, and costs. The full health economic evaluation has not been conducted and will be presented separately. In both trial groups, therapy compliance was defined in five categories: did not use the study drug; poor (1–91 pills taken); moderate (92–299 pills); good (≥300 pills); and complete therapy (all 364 pills or uninterrupted use until the primary endpoint was reached). This count was predominantly determined by returned study drug; however, if patients did not return their drugs or only partially returned them, they were asked to indicate how many days per week and for what period the drug was taken. Patients in categories four and five were considered compliant. Safety outcomes were adverse events (side-effects of the study drug) and serious adverse events. A masked adjudication committee of two gastroenterologists (JEvH, EJvS) evaluated all primary endpoints individually. Disagreements were resolved in a consensus meeting. Serious adverse events were reported by treating clinicians to the coordinating investigators, who reported the events annually to the Dutch Central Committee for Research Involving Human Subjects. A masked and independent reviewer assessed patient safety after 50% of the patients had completed 6 months of treatment.

Statistical analysis

Based on an expected reduction in symptomatic gallstone disease from 11% to 5·5% with a two-sided α of 5%, power of 80%, and drop-out of 20%, we calculated a total sample size of 980 patients.[17] The reported analyses were done in the predefined modified intention-to-treat (ITT) population (ie, the analysis set of all randomly assigned eligible patients with any post-randomisation measurement). Proportions and relative risk (RR) with corresponding 95% CIs are presented for the primary endpoint with testing for significance based on the χ^2 test. As prespecified, we did a formal test of interaction using logistic regression to assess whether treatment effects differed significantly between predefined subgroups (ie, stratification groups). Supervised stepwise backward elimination was used to derive a final model. The main effect (a lower-order term) was maintained in the model, significant or not, for any significant interaction term (higher-order term). A prespecified sensitivity analysis of the primary endpoint in four other predefined analysis sets, with an increasing compliance rate or earlier initiation of the study drug in each successive analysis set, was also done (see statistical analysis plan for detailed information).[18] For secondary endpoints, we also used the χ^2 test to compare the distributions of categorical variables. Kaplan-Meier disease-free survival curves were constructed for the time to symptomatic gallstone disease and cholecystectomy, and Cox-regression analysis was used to test the differences. Based on the EQ-5D-5L scoring profiles, health utility scores were derived from a readily available scoring algorithm for the Netherlands.[22] A generalised linear mixed model, with adjustment for the baseline health utility score and a Toeplitz variance-covariance structure, was used to evaluate differences over time. Quality of life was assessed with the RAND-36 and details are provided in the appendix (p 3). For the safety analysis, we analysed all patients who started at least one dose of ursodeoxycholic acid or placebo and computed a bias-corrected and accelerated bootstrap CI,

drawing 1000 samples of the same size as the original groups and with replacement. As planned, we evaluated if the timing of the initiation of the study drug and therapy compliance influenced the efficacy of ursodeoxycholic acid, and if the contrast between the groups was stable across different time windows of postoperative ultrasonography. Furthermore, two post-hoc exploratory logistic regression analyses of the primary endpoint were done to account for significant baseline differences and variables of known clinical importance (ie, presence of type 2 diabetes, health utility score, age, gender, statin use at baseline, observed therapy compliance [compliant versus non-compliant], and percentage total weight loss at 6 months). Lastly, post-hoc sensitivity analyses were done by imputing missing primary endpoint values and missing postoperative ultrasonography data (appendix pp 3–4). We considered a two-sided p value of less than 0·05 to be statistically significant and did not adjust p values for multiple testing. Hence, all results for gallstone-related secondary endpoints should not be used to infer definitive treatment effects. For statistical analysis we used SPSS statistics for Windows (version 26). The trial is registered with the Netherlands Trial Register, NL5954.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Jan 11, 2017 and Oct 22, 2018, 3272 patients were assessed for eligibility. 985 patients were enrolled and randomly assigned to receive ursodeoxycholic acid (n=492) or placebo (n=493). 13 patients did not receive the allocated treatment because they were ineligible, and five patients did not have any post-randomisation measurement because they immediately withdrew informed consent or were lost to follow-up, leaving 967 patients in the modified ITT population (477 in the ursodeoxycholic acid group and 490 in the placebo group). Two patients in the ursodeoxycholic acid group and six patients in the placebo group had incomplete follow-up that precluded primary endpoint assessment at 24 months (figure 1). The baseline characteristics of the patients were well balanced across the groups except for type 2 diabetes and health utility score (table 1). One-fifth of the patients were diagnosed with asymptomatic gallstones at baseline and 889 (92%) patients received a laparoscopic RYGB. The mean percentage total weight loss did not differ between the groups and was 23·0% (SD 5·4) at 6 months, 29·5% (7·4) at 12 months, and 29·4% (8·9) at 24 months, respectively. In the ursodeoxycholic acid group, 297 (62%) patients and 313 (64%) patients in the placebo group were compliant (RR 0·97, 95% CI 0·89–1·07, p=0·60; appendix p 11). Patients with a RYGB were more often compliant than patients with a sleeve gastrectomy (64% [573 patients] *vs* 48% [37 patients], p=0·0028). The median duration of follow-up was 734 days (IQR 731–741).

	UDCA group	Placebo group	Relative risk (95% CI)	p value
Primary endpoint				
Symptomatic gallstone disease*	31/475 (6·5%)	47/484 (9·7%)	0·67 (0·43–1·04)	0·071
Biliary colic	27/475 (5·7%)	36/484 (7·4%)	..	..
Acute cholecystitis	2/475 (0·4%)	5/484 (1·0%)	..	..
Biliary pancreatitis	1/475 (0·2%)	3/484 (0·6%)	..	..
Choledocholithiasis	1/475 (0·2%)	3/484 (0·6%)	..	..
Secondary endpoints				
Cholecystectomy*	25/475 (5·3%)	44/484 (9·1%)	0·58 (0·36–0·93)	0·022
Presence of gallstones or sludge on postoperative ultrasonography†	112/419 (26·7%)	138/415 (33·3%)	0·80 (0·65–0·99)	0·040

Data are n/N (%), unless otherwise specified. UDCA=ursodeoxycholic acid. *Endpoint assessment was missing in two patients in the UDCA group, and in six patients in the placebo group. †Postoperative ultrasonography was missing in 58 patients in the UDCA group, and in 75 patients in the placebo group. The numbers include patients with symptomatic gallstone disease, patients who had a cholecystectomy, or both.

Table 2: **Gallstone-related primary and secondary endpoints**

The primary endpoint of symptomatic gallstone disease within 24 months occurred in 31 (6·5%) of 475 patients in the ursodeoxycholic acid group and in 47 (9·7%) of 484 patients in the placebo group (RR 0·67, 95% CI 0·43–1·04, p=0·071). In both groups, most of these patients experienced biliary colic (table 2). In the predefined subgroup analysis, logistic regression showed a significant interaction between ursodeoxycholic acid and the presence of asymptomatic gallstones at baseline (adjusted odds ratio [OR] 2·83, 95% CI 1·02–7·86, p=0·046), with no effect of ursodeoxycholic acid in patients with asymptomatic gallstones at baseline and an effect in patients without gallstones at baseline (appendix p 13).

In patients without gallstones at baseline, symptomatic gallstone disease within 24 months occurred in 16 (4·2%) of 381 patients in the ursodeoxycholic acid group compared with 35 (8·9%) of 392 in the placebo group (RR 0·47, 95% CI 0·26–0·84, p=0·0081; table 3). In patients with asymptomatic gallstones at baseline, symptomatic gallstone disease within 24 months occurred in 15 (16·0%) of 94 patients in the ursodeoxycholic acid group compared with 12 (13·0%) of 92 patients in the placebo group (RR 1·22, 95% CI 0·61–2·47, p=0·57). The effect of ursodeoxycholic acid in patients without gallstones at baseline was robust and increased with every successive analysis set in the prespecified sensitivity analysis (appendix p 6). Similar results were found in the imputed datasets (appendix p 5). Although logistic regression showed no significant interaction between ursodeoxycholic acid and the type of surgery (p for interaction 0·19), the use of ursodeoxycholic acid was beneficial in patients who underwent RYGB (RR 0·61, 95% CI 0·38–0·98, p=0·039), but undetermined in

	Patients without gallstones at baseline				Patients with asymptomatic gallstones at baseline			
	UDCA group	Placebo group	Relative risk (95% CI)	p value	UDCA group	Placebo group	Relative risk (95% CI)	p value
Primary endpoint								
Symptomatic gallstone disease*	16/381 (4·2%)	35/392 (8·9%)	0·47 (0·26–0·84)	0·0081	15/94 (16·0%)	12/92 (13·0%)	1·22 (0·61–2·47)	0·57
Secondary endpoints								
Cholecystectomy*	14/381 (3·7%)	35/392 (8·9%)	0·41 (0·23–0·75)	0·0027	11/94 (11·7%)	9/92 (9·8%)	1·20 (0·52–2·75)	0·67
Presence of gallstones or sludge on postoperative ultrasonography†	36/331 (10·9%)	71/338 (21·0%)	0·52 (0·36–0·75)	0·0004	..	..	..	..

Data are n/N (%), unless otherwise specified. p for interaction: 0·046. UDCA=ursodeoxycholic acid. *Endpoint assessment was missing in five patients without gallstones at baseline (two patients in the UDCA group and three patients in the placebo group), and in three patients with asymptomatic gallstones at baseline (all in the placebo group). †Postoperative ultrasonography was missing in 109 patients without gallstones at baseline (52 patients in the UDCA group and 57 patients in the placebo group), and in 24 patients with asymptomatic gallstones at baseline (six patients in the UDCA group and 18 patients in the placebo group).

Table 3: **Outcome according to gallstones at baseline subgroup**

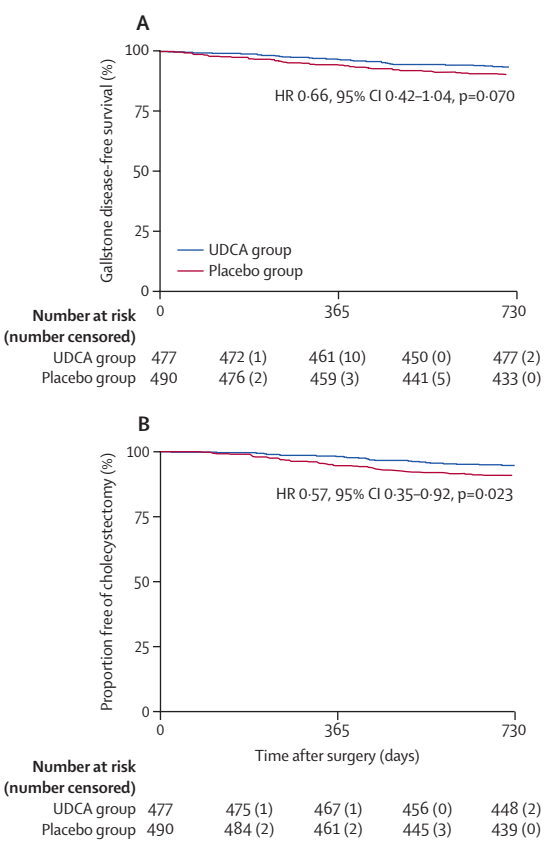

Figure 2: **Kaplan-Meier plots of time to symptomatic gallstone disease (A) and time to cholecystectomy (B)**
HR=hazard ratio. UDCA=ursodeoxycholic acid.

patients who underwent sleeve gastrectomy (1·32, 0·38–4·54, p=0·66; appendix p 16). In patients without gallstones at baseline who underwent RYGB, the risk of symptomatic gallstone disease was lower with ursodeoxycholic acid than with placebo (0·37, 0·20–0·71, p=0·0016; appendix p 17). The two baseline differences (the presence of type 2 diabetes and health utility score) and the other variables of clinical importance were found to have no impact on the beneficial effect of ursodeoxycholic acid (appendix p 6).

Cholecystectomy within 24 months was done in 25 (5·3%) of 475 patients in the ursodeoxycholic acid group and in 44 (9·1%) of 484 patients in the placebo group (RR 0·58, 95% CI 0·36–0·93, p=0·022; table 2). Cholecystectomy was delayed in 12 (six each in the ursodeoxycholic acid and placebo groups) symptomatic patients with biliary colic and done without meeting the definition for symptomatic gallstone disease in three patients (placebo group; appendix p 5). In the ursodeoxycholic acid group, 95% of the patients were free of symptomatic gallstone disease until 481 days of follow-up, and free of cholecystectomy until 657 days. In the placebo group, 95% of the patients were free of symptomatic gallstone disease until 311 days, and free of cholecystectomy until 354 days (figure 2). 834 (86·2%) patients underwent postoperative ultrasonography (table 2). Gallstones or sludge were present in 112 (26·7%) of 419 patients in the ursodeoxycholic acid group and 138 (33·3%) of 415 patients in the placebo group (RR 0·80, 95% CI 0·65–0·99, p=0·040). In patients without gallstones at baseline, the risk of gallstone formation was lower with ursodeoxycholic acid than with placebo (0·52, 0·36–0·75, p=0·0004; table 3). The appendix (p 5) contains the results following multiple imputation. Corrected for baseline health utility score, only the health utility score at 18 months differed significantly between the trial groups (estimated mean difference 0·02, 95% CI 0·001–0·04, p=0·042), in favour of the ursodeoxycholic acid group. Uncorrected health utility scores over time are illustrated in the appendix (p 7). In both trial groups, health-related quality of life was improved after bariatric surgery (appendix p 5). The appendix (pp 5–6) contains results of the additional analyses (eg, to determine whether the timing of the initiation of the study drug

and therapy compliance influenced the efficacy of ursodeoxycholic acid, and whether the contrast between the groups was stable across different time windows of postoperative ultrasonography).

Adverse events were rare. In the ursodeoxycholic acid group, diarrhoea occurred in four (0·9%) of 444 patients and skin rash in two (0·5%) patients. In the placebo group, diarrhoea occurred in two (0·4%) of 453 patients and skin rash in two (0·4%) patients. The total number of serious adverse events did not significantly differ between the trial groups (75 [17%] in 444 patients in the ursodeoxycholic acid group and 102 [23%] in 453 patients in the placebo group). The most common serious adverse events were abdominal pain and internal hernia. No serious adverse event was attributed to the study drug (appendix pp 19–20). There were three deaths in the safety population, two in the ursodeoxycholic acid group, and one in the placebo group. None of the deaths were surgery or treatment-related, and all three occurred after 6 months of follow-up.

Discussion

This multicentre, randomised, superiority trial showed that ursodeoxycholic acid prophylaxis did not significantly reduce the occurrence of symptomatic gallstone disease after bariatric surgery, compared with placebo. However, in patients without gallstones at baseline, ursodeoxycholic acid prophylaxis resulted in a clinically relevant reduction of symptomatic gallstone disease. In those patients, the number needed to treat (NNT) to avoid one patient from having symptomatic gallstone disease was 21. The effect of ursodeoxycholic acid was increased in patients without gallstones at baseline undergoing RYGB (NNT 17), whereas the subgroup of patients undergoing sleeve gastrectomy was too small to draw clear conclusions.

Our trial further supports the existing evidence that ursodeoxycholic acid reduces gallstone formation.[7,8,23–26] However, we did not observe a effect of ursodeoxycholic acid in patients with asymptomatic gallstones at baseline, and with an RR above unity (RR 1·22), it is unlikely that a sufficiently powered subgroup analysis would show such an effect. Asymptomatic gallstones are identified in approximately 10–20% of patients scheduled for bariatric surgery.[11,27–29] Although it is still debated whether ursodeoxycholic acid can reduce the risk of biliary colic in patients with gallstones,[16,30–32] our trial suggests that ursodeoxycholic acid is only able to reduce the formation of new gallstones, and is not able to prevent asymptomatic gallstones becoming symptomatic after bariatric surgery. Furthermore, although logistic regression did not show a significant interaction between the intervention and type of surgery, we did not observe a beneficial effect of ursodeoxycholic acid in patients with sleeve gastrectomy. In our trial, less than 10% of the enrolled patients (n=78) underwent a sleeve gastrectomy. Although sleeve gastrectomy has become the most commonly performed bariatric intervention worldwide, RYGB is still the most performed intervention in Netherlands. Given the small number of patients and poor treatment compliance in patients who underwent sleeve gastrectomy, a relevant protective effect of ursodeoxycholic acid is still possible and no definite conclusions can be drawn for this subgroup. The effect of ursodeoxycholic acid in patients without gallstones at baseline was stronger in those undergoing RYGB than in the overall population of those undergoing RYGB and sleeve gastrectomy. Based on these findings, we consider the use of ursodeoxycholic acid desirable in patients who do not have gallstones before undergoing RYGB. As a consequence, routine preoperative gallbladder ultrasonography should be done to determine the absence of gallstones. The post-hoc sensitivity analyses using a conservative strategy for imputing the missing primary endpoint values and missing postoperative ultrasonography data resulted in similar results as compared with the analyses including all patients for whom data regarding these endpoints were available.

This trial also suggests that the risk of cholecystectomy is lower with ursodeoxycholic acid than with placebo. Cholecystectomy is indicated in all symptomatic patients to prevent recurrent symptoms and gallstone-related complications. However, differentiating between non-specific abdominal complaints and symptomatic gallstone disease can be challenging, especially in a bariatric population.[33] First, the probability of detecting gallstones during imaging after bariatric surgery is high (eg, present in 33·3% of patients in the placebo group in the trial). Second, abdominal pain and other gastrointestinal complaints are very common after bariatric surgery.[34] Accordingly, we observed that three patients underwent cholecystectomy without meeting the definition for symptomatic gallstone disease according to the adjudication committee. Yet, we speculate that, by halving the incidence of gallstones after bariatric surgery, the prescription of ursodeoxycholic acid can simplify the diagnostic workup of abdominal complaints after bariatric surgery and prevent unnecessary cholecystectomies in case of non-specific abdominal complaints.

Poor compliance to preventive treatment is well known, and evidently a concern in patients undergoing bariatric surgery. The moderate overall compliance of 63% in our trial is consistent with compliance rates reported in other trials,[6,8,35,36] although higher rates have been reported as well.[7,25,37,38] Side-effects and compliance were similar in both trial groups, indicating that patients undergoing bariatric surgery experienced difficulty in tolerating either the size or structure of the tablet, rather than the content.[8,37,38] Patients with a sleeve gastrectomy were more often non-compliant than patients with a RYGB. This difference might be explained by the slower recovery after sleeve gastrectomy. The ingestion of large tablets in the early postoperative period is complicated by nausea and dysphagia, two common complaints during the first

months after bariatric surgery. Nevertheless, efforts to improve overall therapy compliance should be made since it influences the efficacy of ursodeoxycholic acid as shown by the sensitivity analysis. Although the two per-protocol sets indicated similar outcomes with initiation of ursodeoxycholic acid within 2 weeks of surgery instead of 8 weeks, we would recommend starting ursodeoxycholic acid as early as clinically possible, given the rapid weight loss directly after surgery.

Strengths of our trial include its double-blind, randomised design, the inclusion of patients with asymptomatic gallstones at baseline, and the assessment of a clinically relevant endpoint by an independent masked adjudication committee. Moreover, the result of pre-operative ultrasonography was blinded for the patients and clinicians. Finally, we aimed to provide a realistic representation of daily clinical practice to facilitate extrapolation and implementation of our study results. Therefore, therapy compliance was not stimulated by frequent positive enforcement and patients had the possibility to postpone the initiation of the study drug until week 8 in case of difficulties tolerating liquids, foods, or drugs.

The results of this trial should be interpreted in view of some limitations. First, our results cannot be extrapolated to patients undergoing sleeve gastrectomy. Although the mechanisms of weight loss differ between RYGB and sleeve gastrectomy, the actual weight loss, which predisposes patients undergoing bariatric surgery to gallstones formation, is almost comparable.[39] Consequently, similar incidences of symptomatic gallstone disease,[40] and a similar effect of ursodeoxycholic acid on gallstone formation are reported.[7,23,24,26] However, whether ursodeoxycholic acid is also able to reduce the occurrence of symptomatic gallstone disease after sleeve gastrectomy is uncertain, and this should ideally be confirmed in a second prospective study that is adequately powered to assess the efficacy of ursodeoxycholic acid in patients undergoing sleeve gastrectomy. Second, although the Kaplan-Meier curves do not indicate a reduction of the beneficial effect of ursodeoxycholic acid over time and weight loss already stabilises after approximately 12 months, the effect of ursodeoxycholic acid on the incidence of symptomatic gallstone after 24 months is uncertain as we limited the follow-up to 24 months.

In summary, this trial showed that ursodeoxycholic acid prophylaxis did not significantly reduce the occurrence of symptomatic gallstone disease in all patients after bariatric surgery. However, in patients without gallstones before RYGB surgery, ursodeoxycholic acid treatment reduced the occurrence of symptomatic gallstone disease compared with placebo. Further research is needed to assess the efficacy of ursodeoxycholic acid after sleeve gastrectomy.

Contributors

RPV and VEAG supervised the trial. SH and MSSG coordinated the trial during inclusion and follow-up. SH did the statistical analysis under the supervision of MGWD. SH drafted the manuscript. MSSG, MGWD, VEAG, and RPV co-authored the manuscript. All authors critically assessed the study design, included patients, or interpreted the data in the study, and edited, read, and approved the final manuscript. All authors had full access to all study data and RPV had final responsibility for the decision to submit for publication.

Declaration of interests

PF reports a grant from the Netherlands Organization for Health Research and Development, during the conduct of the trial. VEAG reports grants from the Foundation for Clinical Research of the Slotervaart Hospital and the Spaarne Gasthuis Academy, during the conduct of the trial. RPV reports grants from Amsterdam Gastroenterology Endocrinology Metabolism, during the conduct of the trial. Zambon Netherlands BV provided trial materials consisting of all ursodeoxycholic acid tablets and an ultrasonography device. All other authors declare no competing interests.

Data sharing

Requests for data can be made to the corresponding author. De-identified individual participant data that underlie the results in this Article and a data dictionary will be shared after approval by an independent review board. Data will be made available after all intended secondary analyses are done and all manuscripts have been accepted for publication. The trial protocol (https://bmcgastroenterol.biomedcentral.com/articles/10.1186/s12876-017-0674-x) and statistical analysis plan (https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-020-04605-7) are already available online.

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References

1 Afshin A, Forouzanfar MH, Reitsma MB, et al. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med* 2017; **377:** 13–27.

2 WHO. Obesity and overweight fact sheet. 2021. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (accessed Dec 17, 2020).

3 Colquitt JL, Pickett K, Loveman E, Frampton GK. Surgery for weight loss in adults. *Cochrane Database Syst Rev* 2014; **8:** CD003641.

4 Welbourn R, Hollyman M, Kinsman R, et al. Bariatric surgery worldwide: baseline demographic description and one-year outcomes from the fourth IFSO Global registry report 2018. *Obes Surg* 2019; **29:** 782–95.

5 Lammert F, Gurusamy K, Ko CW, et al. Gallstones. *Nat Rev Dis Primers* 2016; **2:** 16024.

6 Adams LB, Chang C, Pope J, Kim Y, Liu P, Yates A. Randomized, prospective comparison of ursodeoxycholic acid for the prevention of gallstones after sleeve gastrectomy. *Obes Surg* 2016; **26:** 990–94.

7 Nabil TM, Khalil AH, Gamal K. Effect of oral ursodeoxycholic acid on cholelithiasis following laparoscopic sleeve gastrectomy for morbid obesity. *Surg Obes Relat Dis* 2019; **15:** 827–31.

8 Sakran N, Dar R, Assalia A, et al. The use of Ursolit for gallstone prophylaxis following bariatric surgery: a randomized-controlled trial. *Updates Surg* 2020; **72:** 1125–33.

9 Altieri MS, Yang J, Nie L, Docimo S, Talamini M, Pryor AD. Incidence of cholecystectomy after bariatric surgery. *Surg Obes Relat Dis* 2018; **14:** 992–96.

10 Coupaye M, Calabrese D, Sami O, Msika S, Ledoux S. Evaluation of incidence of cholelithiasis after bariatric surgery in subjects treated or not treated with ursodeoxycholic acid. *Surg Obes Relat Dis* 2017; **13:** 681–85.

11 Portenier DD, Grant JP, Blackwood HS, Pryor A, McMahon RL, DeMaria E. Expectant management of the asymptomatic gallbladder at Roux-en-Y gastric bypass. *Surg Obes Relat Dis* 2007; **3:** 476–79.

12 European Association for the Study of the Liver (EASL). EASL clinical practice guidelines on the prevention, diagnosis and treatment of gallstones. *J Hepatol* 2016; **65:** 146–81.

13 Mechanick JI, Apovian C, Brethauer S, et al. Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures—2019 update: cosponsored by American Association of Clinical Endocrinologists/American College of Endocrinology, The Obesity Society, American Society for Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists. *Surg Obes Relat Dis* 2020; **16:** 175–247.

14 Stokes CS, Gluud LL, Casper M, Lammert F. Ursodeoxycholic acid and diets higher in fat prevent gallbladder stones during weight loss: a meta-analysis of randomized controlled trials. *Clin Gastroenterol Hepatol* 2014; **12:** 1090–1100.

15 Uy MC, Talingdan-Te MC, Espinosa WZ, Daez ML, Ong JP. Ursodeoxycholic acid in the prevention of gallstone formation after bariatric surgery: a meta-analysis. *Obes Surg* 2008; **18:** 1532–38.

16 Tomida S, Abei M, Yamaguchi T, et al. Long-term ursodeoxycholic acid therapy is associated with reduced risk of biliary pain and acute cholecystitis in patients with gallbladder stones: a cohort analysis. *Hepatology* 1999; **30:** 6–13.

17 Boerlage TCC, Haal S, Maurits de Brauw L, et al. Ursodeoxycholic acid for the prevention of symptomatic gallstone disease after bariatric surgery: study protocol for a randomized controlled trial (UPGRADE trial). *BMC Gastroenterol* 2017; **17:** 164.

18 Haal S, Guman MSS, de Brauw LM, et al. Ursodeoxycholic acid for the prevention of symptomatic gallstone disease after bariatric surgery: statistical analysis plan for a randomised controlled trial (UPGRADE trial). *Trials* 2020; **21:** 676.

19 EuroQol Research Foundation. EQ-5D-5L user guide. 2019. https://euroqol.org/publications/user-guides (accessed Dec 17, 2020).

20 Van der Zee KI, Sanderman R. Het meten van de algemene gezondheidstoestand met de RAND-36. 2012. https://www.researchgate.net/publication/283996758_Het_meten_van_de_algemene_gezondheidstoestand_met_de_RAND-36 (accessed Dec 17, 2020).

21 VanderZee KI, Sanderman R, Heyink JW, de Haes H. Psychometric qualities of the RAND 36-Item Health Survey 1.0: a multidimensional measure of general health status. *Int J Behav Med* 1996; **3:** 104–22.

22 Versteegh MM, Vermeulen KM, Evers SMAA, de Wit GA, Prenger R, Stolk EA. Dutch Tariff for the five-level version of EQ-5D. *Value Health* 2016; **19**: 343–52.

23 Coupaye M, Calabrese D, Sami O, Siauve N, Ledoux S. Effectiveness of ursodeoxycholic acid in the prevention of cholelithiasis after sleeve gastrectomy. *Obes Surg* 2019; **29:** 2464–69.

24 Magouliotis DE, Tasiopoulou VS, Svokos AA, et al. Ursodeoxycholic acid in the prevention of gallstone formation after bariatric surgery: an updated systematic review and meta-analysis. *Obes Surg* 2017; **27:** 3021–30.

25 Pizza F, D'Antonio D, Lucido FS, et al. The role of ursodeoxycholic acid (UDCA) in cholelithiasis management after one anastomosis gastric bypass (OAGB) for morbid obesity: results of a monocentric randomized controlled trial. *Obes Surg* 2020; **30:** 4315–24.

26 Talha A, Abdelbaki T, Farouk A, Hasouna E, Azzam E, Shehata G. Cholelithiasis after bariatric surgery, incidence, and prophylaxis: randomized controlled trial. *Surg Endosc* 2020; **34:** 5331–37.

27 D'Hondt M, Sergeant G, Deylgat B, Devriendt D, Van Rooy F, Vansteenkiste F. Prophylactic cholecystectomy, a mandatory step in morbidly obese patients undergoing laparoscopic Roux-en-Y gastric bypass? *J Gastrointest Surg* 2011; **15:** 1532–36.

28 Mishra T, Lakshmi KK, Peddi KK. Prevalence of cholelithiasis and choledocholithiasis in morbidly obese south Indian patients and the further development of biliary calculus disease after sleeve gastrectomy, gastric bypass and mini gastric bypass. *Obes Surg* 2016; **26:** 2411–17.

29 Tucker ON, Fajnwaks P, Szomstein S, Rosenthal RJ. Is concomitant cholecystectomy necessary in obese patients undergoing laparoscopic gastric bypass surgery? *Surg Endosc* 2008; **22:** 2450–54.

30 Meredith TJ, Williams GV, Maton PN, Murphy GM, Saxton HM, Dowling RH. Retrospective comparison of 'Cheno' and 'Urso' in the medical treatment of gallstones. *Gut* 1982; **23:** 382–89.

31 Tint GS, Salen G, Colalillo A, et al. Ursodeoxycholic acid: a safe and effective agent for dissolving cholesterol gallstones. *Ann Intern Med* 1982; **97:** 351–56.

32 Venneman NG, Besselink MG, Keulemans YC, et al. Ursodeoxycholic acid exerts no beneficial effect in patients with symptomatic gallstones awaiting cholecystectomy. *Hepatology* 2006; **43:** 1276–83.

33 de Jong JJ, Latenstein CSS, Boerma D, et al. Functional dyspepsia and irritable bowel syndrome are highly prevalent in patients with gallstones and are negatively associated with outcomes after cholecystectomy: a prospective, multicentre, observational study (PERFECT trial). *Ann Surg* 2020; published online Sept 1. https://doi.org/10.1097/SLA.0000000000004453.

34 Boerlage TCC, Westerink F, van de Laar AWJM, Hutten BA, Brandjes DPM, Gerdes VEA. Gastrointestinal symptoms before and after laparoscopic Roux-en-Y gastric bypass: a longitudinal assessment. *Surg Obes Relat Dis* 2019; **15:** 871–77.

35 Williams C, Gowan R, Perey BJ. A double-blind placebo-controlled trial of ursodeoxycholic acid in the prevention of gallstones during weight loss after vertical banded gastroplasty. *Obes Surg* 1993; **3:** 257–59.

36 Wudel LJ Jr, Wright JK, Debelak JP, Allos TM, Shyr Y, Chapman WC. Prevention of gallstone formation in morbidly obese patients undergoing rapid weight loss: results of a randomized controlled pilot study. *J Surg Res* 2002; **102:** 50–56.

37 Miller K, Hell E, Lang B, Lengauer E. Gallstone formation prophylaxis after gastric restrictive procedures for weight loss: a randomized double-blind placebo-controlled trial. *Ann Surg* 2003; **238:** 697–702.

38 Sugerman HJ, Brewer WH, Shiffman ML, et al. A multicenter, placebo-controlled, randomized, double-blind, prospective trial of prophylactic ursodiol for the prevention of gallstone formation following gastric-bypass-induced rapid weight loss. *Am J Surg* 1995; **169:** 91–96.

39 Peterli R, Wölnerhanssen BK, Peters T, et al. Effect of laparoscopic sleeve gastrectomy vs laparoscopic Roux-en-Y gastric bypass on weight loss in patients with morbid obesity: the SM-BOSS randomized clinical trial. *JAMA* 2018; **319:** 255–65.

40 Coupaye M, Castel B, Sami O, Tuyeras G, Msika S, Ledoux S. Comparison of the incidence of cholelithiasis after sleeve gastrectomy and Roux-en-Y gastric bypass in obese patients: a prospective study. *Surg Obes Relat Dis* 2015; **11:** 779–84.