Restrictive strategy versus usual care for cholecystectomy in patients with gallstones and abdominal pain (SECURE): a multicentre, randomised, parallel-arm, non-inferiority trial

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See Comment page 2280

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Summary

Background International guidelines advise laparoscopic cholecystectomy to treat symptomatic, uncomplicated gallstones. Usual care regarding cholecystectomy is associated with practice variation and persistent post-cholecystectomy pain in 10–41% of patients. We aimed to compare the non-inferiority of a restrictive strategy with stepwise selection with usual care to assess (in)efficient use of cholecystectomy.

Methods We did a multicentre, randomised, parallel-arm, non-inferiority study in 24 academic and non-academic hospitals in the Netherlands. We enrolled patients aged 18–95 years with abdominal pain and ultrasound-proven gallstones or sludge. Patients were randomly assigned (1:1) to either usual care in which selection for cholecystectomy was left to the discretion of the surgeon, or a restrictive strategy with stepwise selection for cholecystectomy. For the restrictive strategy, cholecystectomy was advised for patients who fulfilled all five pre-specified criteria of the triage instrument: 1) severe pain attacks, 2) pain lasting 15–30 min or longer, 3) pain located in epigastrium or right upper quadrant, 4) pain radiating to the back, and 5) a positive pain response to simple analgesics. Randomisation was done with an online program, implemented into a web-based application using blocks of variable sizes, and stratified for centre (academic versus non-academic and a high vs low number of patients), sex, and body-mass index. Physicians and patients were masked for study-arm allocation until after completion of the triage instrument. The primary, non-inferiority, patient-reported endpoint was the proportion of patients who were pain-free at 12 months' follow-up, analysed by intention to treat and per protocol. A 5% non-inferiority margin was chosen, based on the estimated clinically relevant difference. Safety analyses were also done in the intention-to treat population. This trial is registered at the Netherlands National Trial Register, number NTR4022.

Findings Between Feb 5, 2014, and April 25, 2017, we included 1067 patients for analysis: 537 assigned to usual care and 530 to the restrictive strategy. At 12 months' follow-up 298 patients (56%; 95% CI 52·0–60·4) were pain-free in the restrictive strategy group, compared with 321 patients (60%; 56·0–63·8) in usual care. Non-inferiority was not shown (difference 3·6%; one-sided 95% lower CI −8·6%; $p_{non\text{-}inferiority}$=0·316). According to a secondary endpoint analysis, the restrictive strategy resulted in significantly fewer cholecystectomies than usual care (358 [68%] of 529 vs 394 [75%] of 536; p=0·01). There were no between-group differences in trial-related gallstone complications (40 patients [8%] of 529 in usual care vs 38 [7%] of 536 in restrictive strategy; p=0·16) and surgical complications (74 [21%] of 358 vs 88 [22%] of 404, p=0·77), or in non-trial-related serious adverse events (27 [5%] of 529 vs 29 [5%] of 526).

Interpretation Suboptimal pain reduction in patients with gallstones and abdominal pain was noted with both usual care and following a restrictive strategy for selection for cholecystectomy. However, the restrictive strategy was associated with fewer cholecystectomies. The findings should encourage physicians involved in the care of patients with gallstones to rethink cholecystectomy, and to be more careful in advising a surgical approach in patients with gallstones and abdominal symptoms.

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Introduction

Symptomatic gallstone disease constitutes a substantial and increasing health problem in Western society.[1,2] Yearly, there are more than 1·8 million ambulatory visits for symptomatic gallstones in the USA.[3] 15% of all patients with cholelithiasis develop complications such as cholecystitis, cholangitis, or biliary pancreatitis.[3] The remaining 95% of patients are at risk for symptoms arising from cholecystolithiasis. Typically, these patients develop episodes of biliary colics, defined by the ROME III criteria as acute severe abdominal pain located in the right upper quadrant or epigastrium lasting 15–30 min or longer.[4] Most patients do not develop typical attacks, but might report non-specific abdominal symptoms.[3,5]

Research in context

Evidence before this study

International guidelines advise laparoscopic cholecystectomy as a treatment for uncomplicated symptomatic cholecystolithiasis. A systematic review published in 2013, two prospective studies published in 2011 and 2017, and the results of two randomised trials published in 2005 showed that 10–41% of all patients following cholecystectomy continued to have abdominal pain. Persistent postoperative pain is associated with a signi cant burden for health-care systems, especially from an economical viewpoint.

A systematic review of international guidelines published in 2017 showed no consensus on the criteria to select patients for elective cholecystectomy. The absence of consensus is further illustrated in studies showing large variation in clinical practice among and within countries. We found no studies or trials assessing di erent criteria for indication of cholecystectomy for uncomplicated symptomatic cholecystolithiasis, or studies assessing the e ectiveness of a more restrictive strategy for selecting patients for cholecystectomy, compared with standard of care.

Added value of this study

Our randomised, controlled, non-inferiority trial (SECURE) in patients with abdominal pain and ultrasound-proven gallstones or sludge compared usual care with a restrictive strategy for selecting patients for cholecystectomy. The restrictive strategy was based on the Rome criteria of biliary colic. The ndings showed that the primary outcome of pain reduction was suboptimal with both usual care and the restrictive strategy (non-inferiority of the restrictive strategy not shown). However, the restrictive strategy was associated with a reduction in cholecystectomies by 7·7% compared with usual care.

Implications of all the available evidence

The SECURE trial illustrates that current surgical treatment of patients with gallstones and abdominal symptoms is far from optimal, and is not improved by implementing a more restrictive selection for cholecystectomy. It is important to realise that most international guidelines on management of cholelithiasis include the Rome criteria as part of the diagnostic selection process for cholecystectomy. These ndings should encourage physicians involved in the care of patients with gallstones to rethink cholecystectomy, and to be more careful in advising a surgical approach in patients with gallstones and abdominal symptoms.

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International guidelines advise laparoscopic cholecystectomy to treat symptomatic cholecystolithiasis,[1–8] resulting in 700 000 cholecystectomies in the USA per year,[3] at estimated costs of US$9 billion.[9] However, a systematic review[10] and multiple prospective cohort studies[11–13] indicate that 10–41% of patients continue to have persistent abdominal pain despite cholecystectomy. As well as a ecting their quality of life, these patients generate a substantial burden for health-care systems, including in economical terms.[13,14]

The indication for cholecystectomy in uncomplicated symptomatic cholecystolithiasis varies globally.[15] There is no consensus on the best criteria to select patients for elective surgery, resulting in preference-sensitive care[16] and large variations in cholecystectomy practices among and within countries.[17–20] This variation emphasises the need for a better diagnostic strategy to select patients with uncomplicated symptomatic cholecystolithiasis for successful cholecystectomy.[21,22] A standardised strategy with stepwise selection for cholecystectomy based on the presence of true biliary symptoms might assist in reducing the number of ine ective cholecystectomies. To this end, we designed a randomised nationwide clinical trial in the Netherlands comparing the e ectiveness of a restrictive standardised strategy with usual care to select patients for cholecystectomy. We hypothesised that the restrictive strategy arm would be non-inferior to usual care in the number of patients being pain-free at 12 months' follow-up at a lower proportion of cholecystectomies.

Methods

Study design and participants

The trial protocol, including study procedures and randomisation[23] and the statistical analysis plan[24] have been published before. Brie y, in this multicentre, randomised, parallel-arm, non-inferiority study (SECURE), patients were enrolled from 24 academic and non-academic hospitals in the Netherlands. The institutional review board of the Academic Medical Center (Amsterdam, Netherlands) approved the study protocol. The local ethical committees and boards of directors of all participating centres endorsed the protocol before local execution of the trial.

Eligible participants were patients aged 18–95 years with abdominal pain and ultrasound-proven gallstones who were referred to a surgical outpatient clinic, and contacted for participation before their rst visit. Symptomatic patients with ultrasound-proven sludge were also eligible for inclusion, because sludge might cause similar symptoms and complications as gallstones,[25,26] and management as for cholecystolithiasis is advised by the Dutch national guidelines.[6] Exclusion criteria were (1) a history of, or indication (physical or sonographic) for complicated cholelithiasis (ie, biliary pancreatitis, cholangitis, common bile duct stones, and cholecystitis); (2) an indication for primary open cholecystectomy; (3) a history of current malignancy; (4) an expected short lifespan of less than 12 months; (5) an American Society of Anesthesiologists physical status classi cation of III and IV; (5) known liver cirrhosis; (6) cognitive disorders that predispose unreliable

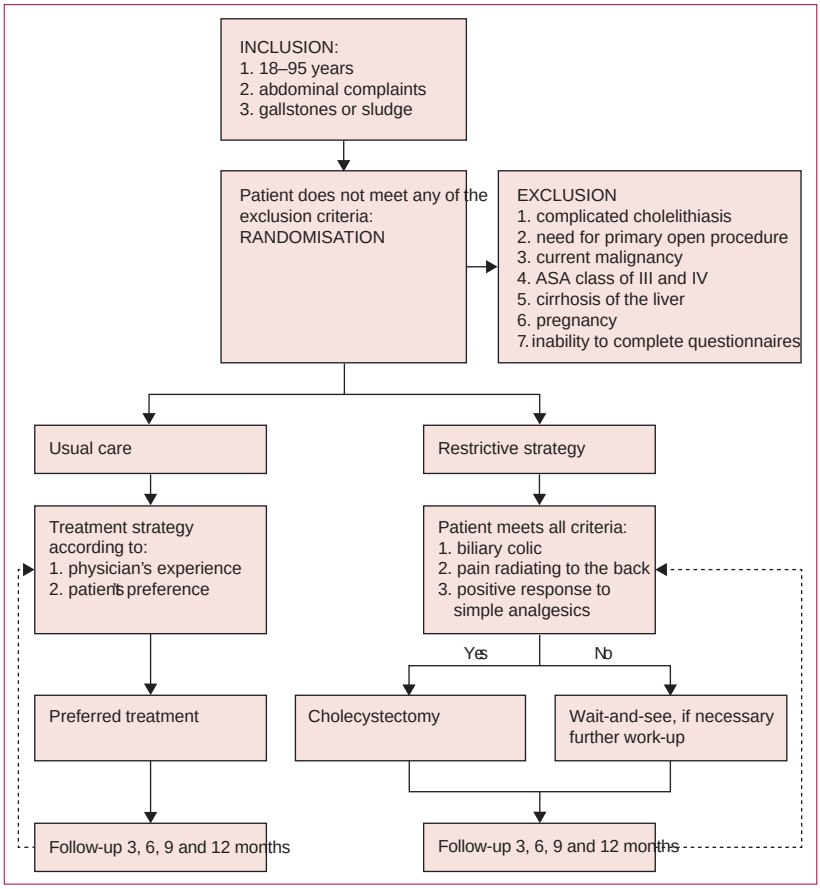

Figure 1: Inclusion, randomisation, and management of SECURE
Biliary colic symptoms were defined as severe steady pain, lasting 15–30 min or longer, usually located in the epigastrium or right upper quadrant, or both. ASA=American Society of Anesthesiologists. Reproduced from de Reuver et al.[23]

questionnaire responses; (7) insufficient knowledge of the Dutch language, and (8) pregnancy. All included patients provided written, informed consent before participation in the trial.

Randomisation and masking

Included patients were randomly assigned (1:1) to either usual care or a restrictive strategy. Randomisation was done with an online computer software program (ALEA NKI-AVL, Amsterdam, The Netherlands, version 2.2) and implemented into a web-based application using blocks of variable sizes. Randomisation was stratified for centre (academic versus non-academic and high versus low volume), sex, and body mass index. Study arm allocation was revealed to physicians and patients after completion of the triage instrument. The statistical analysis plan was designed before the start of the study.[23]

Procedures

Figure 1 shows the flow of patients in the study.[23] Patients were randomly allocated to either usual care or restrictive strategy before their first visit at the surgical outpatients' clinic. At the first visit, for all patients, a triage instrument was filled out in an online patient record form by the treating physician in consultation with the patient. In this consultation it was assessed whether included patients fulfilled five pre-specified criteria[23] for symptomatic cholecystolithiasis: 1) severe pain attacks, 2) pain lasting 15–30 min or longer, 3) pain located in epigastrium or right upper quadrant, 4) pain radiating to the back, and 5) a positive pain response to simple analgesics. These five criteria were formulated based on systematic reviews of the literature that showed that biliary colic (defined by Rome III criteria),[4] pain radiating to the back, and a positive response to simple analgesics have a significant association with diagnosis of symptomatic cholecystolithiasis.[5,27] According to several international and national guidelines on gallstone disease, these are the symptoms indicating cholecystectomy.[6–8]

The study group allocation was revealed to patient and physician only after completion of the triage instrument. In the usual care arm, no summary result of the triage instrument was presented, and treatment advice was not given. Patients assigned to the usual care arm received the standard care given in the participating centres, and selection for cholecystectomy was left to the discretion of the surgeon. In the restrictive strategy arm, advice to do a cholecystectomy was displayed by the triage instrument in patients who fulfilled all five pre-specified criteria of the triage instrument. Patients in the restrictive strategy arm who did not meet the pre-specified criteria were selected for conservative treatment and for further work-up in search of an alternative diagnosis of abdominal symptoms. The diagnosis and treatment of possible alternative conditions was left to the discretion of the treating physician. The work-up, abdominal symptoms, and effect of treatment were assessed at the outpatient clinics. At each follow-up visit, in patients without fulfilment of all five triage criteria in the restrictive strategy group indication for cholecystectomy was reconsidered, and if rejected, conservative treatment was continued.

The patient-reported outcomes of both study arms were assessed during follow-up using questionnaires. All patients completed the study questionnaire at baseline and at 3, 6, 9, and 12 months' follow-up. The questionnaire was composed from the EuroQol 5 Dimensions (EQ-5D-3L), the Short-Form Health and Labour Questionnaire (SF-HLQ),[28] Izbicki Pain Score,[29] GastroIntestinal Quality of Life Index (GIQLI),[30,31] and the Gallstone symptom list.[32] Details on the content of the questionnaires are in the study protocol.[23] The analgesics included in the Izbicki Pain Score were adapted to those commonly used in the Netherlands. Additional data were collected by patients interview by phone and patients' medical records after 12 months' follow-up.

Outcomes

The primary, non-inferiority endpoint was the proportion of patients who were pain-free at 12 months. Pain-free

was defined as an Izbicki Pain Score of 10 or less (with a visual analogue scale [VAS] pain score ≤4). Secondary, superiority endpoints were number of cholecystectomies, time to being pain-free, complications due to gallstones (ie, choledocholithiasis, cholangitis, cholecystitis, biliary pancreatitis, or biliary colic needing hospitalisation) or cholecystectomy (including conversion rate and complications classified according to the Clavien Dindo Classification), patient-reported satisfaction on treatment outcome (Numeric Rating Scale 1–10), alternative diagnostics and treatment, and patients' health status over time (both disease-specific quality of life based on GIQLI, and health utility scores derived from EQ-5D-3L profiles). Supplementary outcomes were the association between the patients' symptoms and treatment outcome. Safety outcomes were complications of cholelithiasis or treatment, and non-trial-related serious adverse events.

Statistical analysis

The detailed power analysis and strategy for patient replacement are in the protocol[23] and statistical analysis plan.[24] The initial sample size calculation was based on the assumptions that 1) the proportion of pain-free patients in the restrictive strategy is at least equal to that in usual care, and 2) the maximum proportion of pain-free patients after usual care is 80%.[10] We considered a non-inferiority boundary of 5% and potential contamination of usual care by restrictive strategy. With a one-sided Z test, power of 80%, and significance level of 5%, a total of 1038 assessable patients needed to be included (519 in each arm). Patients were assessable if they had not been excluded because of eligibility protocol violations (eg, withdrawn informed consent), if the triage instrument at first visit was completed by the treating physician, and the primary outcome at 12 months' follow-up was available (either directly or through imputation). Patients not fulfilling these criteria were replaced.

The primary analysis was done by the one-tailed χ^2 test, comparing the proportions of pain-free patients at 12 month follow-up between the usual care and restrictive strategy groups. Non-inferiority was defined as when the lower limit of the one-sided 95% CI for the proportion of patients being pain-free at 12 months following restrictive strategy was within the absolute 5% margin below the proportion under usual care. The results of the intention to treat (ITT) and per-protocol analyses both had to show non-inferiority of restrictive strategy compared with usual care, to support interpretation. In the per-protocol analysis, patients in the usual care group who were planned for cholecystectomy, but for whom surgery was not done during follow-up were excluded. In the restrictive strategy these were the patients who met the pre-specified criteria of the triage instrument but did not undergo cholecystectomy or who did not meet the pre-specified criteria and did undergo cholecystectomy (except if additional work-up excluded alternative diagnoses).

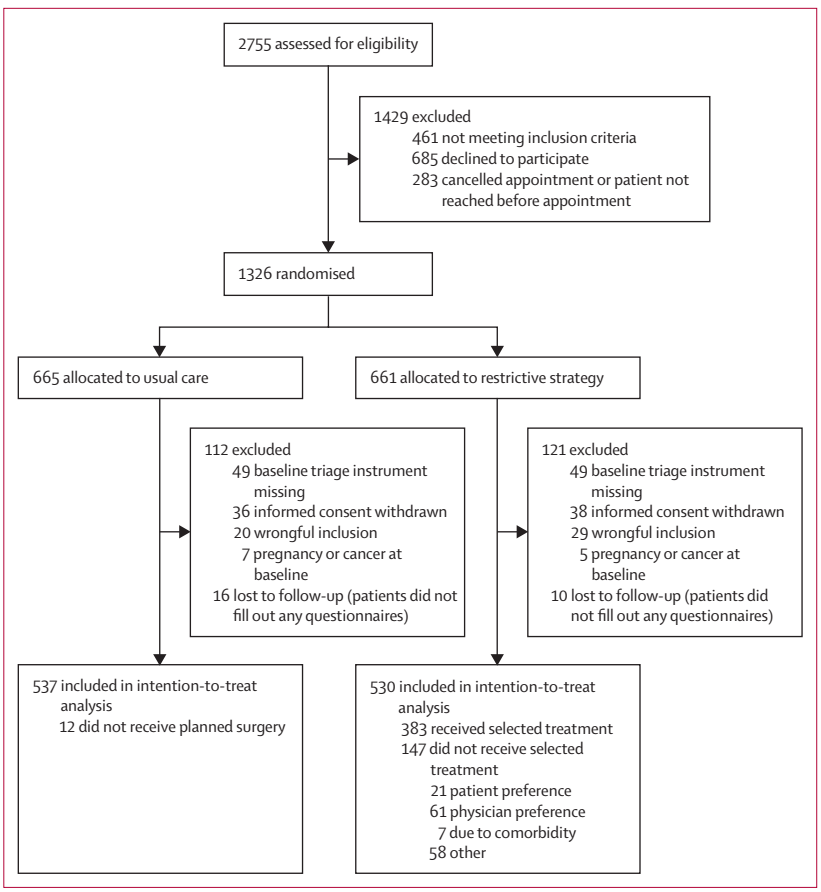

Figure 2: **Trial profile**

Missing data from the primary outcome were imputed using the last observation carried forward (LOCF) strategy. Several methods of imputation were tested and the LOCF imputation strategy had the smallest CIs and the point estimates closest to the complete case analysis. A multiple imputation strategy using predictive mean matching (included variables are in the statistical analysis plan)[24] had a deviation to a high percentage of pain-free patients, and might have overestimated the total proportion of patients being pain-free. For secondary outcomes, we did multiple imputations using predictive mean matching to impute missing values of all questionnaires on all timepoints. The number of patients with imputed missing values were reported per secondary endpoint.

Secondary endpoints and safety analyses were analysed in the ITT population. Analyses were done using the χ^2 test for dichotomous data, an independent *t* test for normally distributed continuous data, and the Mann-Whitney test for skewed continuous data. Testing for normality of data distributions was based on the Shapiro-Wilks test. Data for quality of life were assessed by repeated-measurement analysis using a linear mixed model. Time to being free from pain was assessed using life tables and Wilcoxon Gehad statistics. In all analyses

	Usual care (n=537)	Restrictive strategy (n=530)
Age (years)	49·0 (39·0–58·0)	48·0 (37·0–59·0)
Sex		
Female	387 (72%)	399/530 (75%)
Male	150 (28%)	131 (25%)
BMI (kg/m²)	27·5 (24·6–31·2)	27·5 (24·5–30·9)
ASA classification II	86 (16%)	81 (15%)
History of abdominal surgery	205 (38%)	196 (37%)
Use of pain medication		
Any	259 (48%)	268 (51%)
Paracetamol	60 (11%)	63 (12%)
NSAID	169 (32%)	161 (30%)
Other	29 (5%)	44 (8%)
Indication for pain medication		
Gallstone symptoms	217/259 (84%)	206/268 (77%)
Other indication	42/259 (16%)	62/268 (23%)
Current smoker	105 (20%)	104 (20%)
Packs per week	3·0 (2·0–5·0)	3·0 (2·0–5·8)
Consumes alcohol	256 (48%)	239 (45%)
Glasses per week	4·0 (2·0–7·0)	4·0 (1·0–7·0)
Baseline Izbicki Pain Score		
Total score*	35·5 (29·0–41·4)	35·0 (28·9–42·5)
VAS pain score†	7·5 (5·4–8·7)	7·5 (5·5–8·8)
Baseline Health Utility score‡	0·84 (0·73–1·00)	0·84 (0·72–1·00)
Baseline GIQLI total score§	108 (94–120)	108 (92–120)

Data are median (IQR), n (%), or n/N (%). BMI=body-mass index. ASA=American Society of Anesthesiologists. NSAID=non-steroidal anti-inflammatory drug. VAS=visual analog scale. GIQLI=Gastrointestinal Quality of Life Index. *Imputed using multiple imputation with predictive mean matching (PMM); 103 missing values before imputation. †Imputed using multiple imputation with PMM; 101 missing values before imputation. ‡Imputed using multiple imputation with PMM; 96 missing values before imputation. §Imputed using multiple imputation with PMM; 110 missing values before imputation.

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

for secondary endpoints and safety analyses, statistical uncertainties were expressed in 95% two-sided CIs. A p value of less than 0·05 indicated statistical significance (further details on the statistical analysis are in the statistical analysis plan).[24] An independent data monitoring and safety committee periodically reviewed safety data. This trial is registered at the Netherlands National Trial Register, number NTR4022.

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. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

See Online for appendix

Results

Between Feb 5, 2014, and April 25, 2017, we included 1067 patients for ITT analysis: 537 allocated to usual care and 530 to the restrictive strategy (figure 2). 525 (98%) of 537 patients allocated to usual care and 383 (72%) of 530 patients allocated to the restrictive strategy were treated per protocol (figure 2).

The baseline characteristics of patients in the usual care and the restrictive strategy groups were similar (table 1). Patients in the restrictive strategy group reported more severe pain attacks as a preoperative symptom than patients in usual care (table 2). The other four pre-specified criteria of the triage instrument did not differ significantly between the two groups. Despite randomisation being done before the triage instrument, and both doctor and patient being unaware of the treatment allocation when filling out the triage instrument, more patients fulfilled all five pre-specified criteria of the baseline triage instrument in the restrictive strategy compared with patients allocated to usual care (table 2).

298 patients (56%, 95% CI, 52·0–60·4) of 530 in the restrictive strategy group and 321 patients (60%, 95% CI 55·6–63·8) of 537 in the usual care group were pain-free at 12 months' follow-up, an absolute difference of 3·6% (one-sided 95% lower CI –8·6%; $p_{non\text{-}inferiority}$=0·316) at the expense of the restrictive strategy (appendix). Non-inferiority of the restrictive strategy within a 5% margin below the proportion of pain-free patients in usual care was therefore not shown. In the per-protocol analysis, non-inferiority was again not shown: 216 (56%, 95% CI 51·4–61·3) of 383 patients in the restrictive strategy and 314 (60%, 95% CI 55·6–63·9) of 525 patients were pain-free at 12 months' follow-up, a difference of –3·4% with a one-sided 95% lower CI of –9·0% ($p_{non\text{-}inferiority}$=0·316). Missing data for the primary endpoint were imputed for 26 patients (5%) in the usual care group and 23 patients (4%) in the restrictive strategy group.

At 12 months' follow-up, of patients who underwent cholecystectomy, the proportion who were pain-free did not differ between the groups (table 3). However, the number of patients who underwent cholecystectomy was lower in the restrictive strategy group than in usual care (7·7% fewer cholecystectomies in the restrictive strategy; table 3). Median time to being pain-free (irrespective of surgical or conservative intervention) was similar for patients in the restrictive strategy and usual care arms (table 3, figure 3). Patient-reported satisfaction with treatment outcome at 12 month follow-up was similar between groups. Patients' health status over time, as assessed by the GIQLI score, also did not differ between groups (p=0·820; figure 4). Patients with preoperative biliary colics were more often pain-free at 12 month follow-up than patients without classic biliary colics (437 [61%] of 717 *vs* 182 [52%] of 350, respectively; p=0·005). These proportions were 379 (66%) of 579 and 105 (57%) of 183, respectively, (p=0·048) when only considering patients who underwent a cholecystectomy (appendix).

There were no between-group differences in trial-related gallstone complications and surgical complications, or in

	Usual care (n=537)	Restrictive strategy (n=530)	p value
Severe pain in attacks*	411 (77%)	440 (83%)	0·008
Located in right upper quadrant or epigastric region*	482 (90%)	493 (93%)	0·058
Pain radiating to the back*	360 (67%)	364 (69%)	0·566
Pain responding to simple analgesics*	289 (54%)	284 (54%)	0·217
Duration of pain longer than 15-30 min*	436 (81%)	447 (84%)	0·174
Continuous pain	165 (31%)	137 (26%)	0·077
Attack of pain more than twice a month	357 (67%)	328 (62%)	0·118
Need to move during attack	361 (67%)	373 (70%)	0·267
Pain radiating to the chest	128 (24%)	137 (26%)	0·447
Intolerance of fatty foods	243 (45%)	250 (47%)	0·530
Nausea and vomiting	308 (57%)	327 (62%)	0·149
Diarrhoea	97 (18%)	92 (17%)	0·763
Di cult defecation	102 (19%)	97 (18%)	0·772
Acid burn	169 (32%)	163 (31%)	0·800
Bloated feeling	277 (52%)	262 (49%)	0·483
Flatulence	179 (33%)	210 (40%)	0·033
Burping	209 (39%)	223 (42%)	0·294
Ful lment of all ve pre-speci ed criteria	152 (28%)	201 (38%)	0·001
Ful lment of at least four pre-speci ed criteria	372 (69%)	397 (75%)	0·040
Ful lment of at least three pre-speci ed criteria	483 (90%)	483 (91%)	0·507

Data are n (%). *One of the ve pre-speci ed criteria for symptomatic cholecystolithiasis of the triage instrument, indicating cholecystectomy in the restrictive strategy.

Table : Preoperative symptoms in all patients

	Usual care (n=536)	Restrictive strategy (n=529)	p value
Cholecystectomy	404/536 (75%)	358/529 (68%)	0·005
Pain-free at 12 months after cholecystectomy	256/404 (63%)	228/358 (64%)	0·927
Time to cholecystectomy (weeks)	6·0 (2·25–11·0)	6·0 (3·0–10·0)	0·744
Conservative treatment	132/536 (25%)	171/529 (32%)	0·005
Pain-free at 12 months after conservative treatment	65/132 (49%)	70/171 (41%)	0·149
Time to being pain free, irrespective of surgical or conservative intervention (months)*	7·29	7·87	0·130
Gallstone complications	38/536 (7%)	40/529 (8%)	0·155
Preoperative and with conservative treatment	33/536 (6%)	33/529 (6%)	0·808
Choledocholithiasis	1/536 (<1%)	7/529 (1%)	..
Acute cholecystitis	10/536 (2%)	5/529 (<1%)	..
Biliary pancreatitis	3/536 (<1%)	3/529 (<1%)	..
Cholangitis	0	0	..
Colic with hospitalisation	19/536 (4%)	18/529 (3%)	..
Postoperative	5/536 (<1%)	7/529 (1%)	0·808
Choledocholithiasis	3/536 (<1%)	6/529 (1%)	..
Biliary pancreatitis	1/536 (<1%)	0	..
Colic with hospitalisation	1/536 (<1%)	1/529 (<1%)	..
Conversion to laparotomy	7/404 (2%)	7/358 (2%)	0·965
Surgical complications	88/404 (22%)	74/358 (21%)	0·769
Clavien Dindo Classi cation	..	..	..
I	27/404 (7%)	29/358 (8%)	..
II	26/404 (6%)	22/358 (6%)	..
IIIa	28/404 (7%)	14/358 (4%)	..
IIIb	7/404 (2%)	7/358 (2%)	..
IV	0	2/358 (<1%)	..
V	0	0	..
Patient-reported satisfaction (numeric rating scale)†	8·4 (8·0–9·0)	8·4 (8·0–9·1)	0·976
Non-trial-related serious adverse events	29/536 (5%)	27/529 (5%)	0·857

Data are n/N (%) or median (IQR). Data on secondary outcomes were unavailable from patients' medical records for one patient in the restrictive strategy group and one patient in the usual care group, resulting in a di erence of one patient per group between the primary and secondary outcomes. *No IQR is reported, because 25% of patients (lower quartile) were pain-free within 6 months; however the upper quartile of 75% of patients pain-free was never reached. †Imputed using multiple imputation with predictive mean matching; 201 missing values before imputation.

Table : Secondary outcomes

non-trial-related serious adverse events. Most gallstone complications occurred preoperatively (table 3).

A cholecystectomy was not done in 303 (28%) of 1067 included patients with gallstones and abdominal pain. Of these patients, 217 (72%) went for an additional visit to a specialist: 118 (39%) visited a surgeon for a second time, 60 (20%) visited a gastroenterologist, and 39 (13%) visited another medical specialist (such as an internist, urologist, or gynaecologist). Additional work-up was done for 123 patients (41%) of the 303 who did not have a cholecystectomy. This included laboratory measurements (63 [20%]), gastroscopy (59 [19%]), colonoscopy (20 [7%]), and CT or MRI (22 [7%]). In 102 patients [34%] of the 303 who did not have a cholecystectomy, an alternative diagnosis for the abdominal symptoms, other than symptomatic gallstones, such as acid re ux or gastritis (in 31 patients [10%] of 303), irritable bowel syndrome (14 [5%] of 303), or functional abdominal pain (12 [4%] of 303) was found.

Discussion

This trial showed suboptimal pain reduction in patients with gallstones and abdominal pain following both usual care and a restrictive strategy for selection for cholecystectomy. Even after cholecystectomy, 37% of patients in both groups continued to have abdominal pain. However, the restrictive strategy was associated with fewer cholecystectomies at 12 months follow-up. Presence of biliary colics before cholecystectomy was associated with better pain relief after cholecystectomy compared with patients without typical biliary colics. We were unable to show advantages of either strategy in terms of median time to pain-free state or health status.

To our knowledge, this study is unique in its aim to assess e ectiveness of a new strategy for patient selection, compared with standard of care for cholecystectomy.

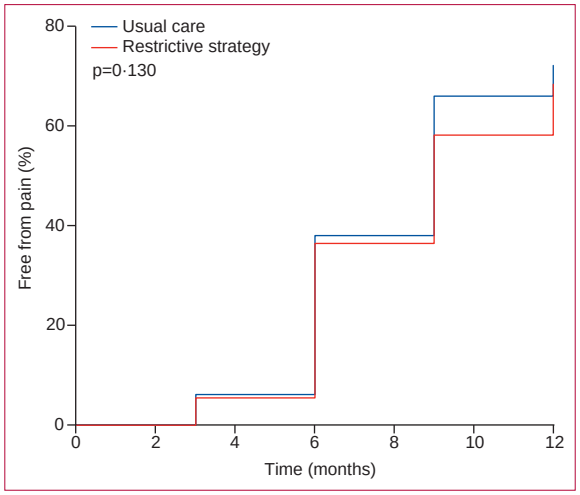

Figure : Time until free from pain
The proportion of patients free from pain in this gure are based on Izbicki pain scores imputed by multiple imputation with predictive mean matching; therefore this proportion is slightly higher than that shown in the primary endpoint imputed with last observation carried forward (LOCF). Because LOCF is the more reliable and conservative method in our case, this was used for the primary endpoint, but could not be used for this gure due to the nature of the analysis.

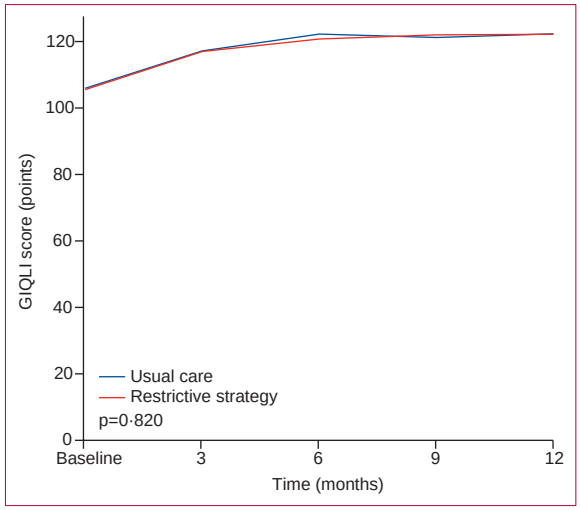

Figure : Health status over time
GIQLI=Gastrointestinal Quality of Life Index.

Most surgical studies compare two operative strategies, or operative versus conservative treatment. Here, we assessed the di erences in indication for operative treatment. One previous randomised trial compared pain in patients after cholecystectomy versus conservative treatment.[32] This trial showed no di erences in pain and quality of life between both groups, with 50% of the patients in the conservative group undergoing surgery at a later time. After a median 61 months' follow-up, 19% of the patients who underwent cholecystectomy reported di use abdominal pain and 8% still had severe painful attacks.[13] This nding is consistent with those from a systematic review that found cholecystectomy relieves pain in 59% to 100% of patients.[10] Our data are at the lower end of the bracket as we noted that 63% of patients were pain-free at 12 months after cholecystectomy. Most studies included in the systematic review were cohort studies, and very heterogeneous regarding inclusion criteria (patients with complicated as well as uncomplicated gallstones), duration of follow-up (3 to 61 months), and measurement of outcome. The heterogeneity makes direct comparison of the outcomes of these studies di cult. A few prospective cohort studies have been done in the Netherlands comparing patient reported outcomes after cholecystectomy, one at 12 and 24 weeks' follow-up,[11,33] one at 61 months' follow-up,[34] and another at a mean of 10 years following cholecystectomy.[35] All these studies showed that around 40% of patients continued to have abdominal pain after cholecystectomy.

Before we started this trial, we hypothesised that the proportion of pain-free patients in the restrictive strategy would be at least equal to that in the usual care group, and we expected that usual care would relieve pain in around 80% of patients.[23] By contrast, we showed that at 12 months after cholecystectomy only around 63% of patients were free from pain, regardless of study group. This nding illustrates that surgical treatment for patients with abdominal symptoms and gallstones is indeed far from optimal, and a more restrictive selection for cholecystectomy is not the solution to the problem. The restrictive strategy, using the Rome criteria of a biliary colic[4,5,27] did not improve selection of patients for cholecystectomy. Almost all international guidelines on clinical management of patients with gallstone disease include the Rome criteria as part of the diagnostic selection process for cholecystectomy. Our data showed that cholecystectomy was more e ective in relieving pain in this subset of patients. However, still 35% of patients with typical biliary colics reported persistent abdominal pain after surgery. This suggests a limited validity of the Rome criteria in the selection of patients for cholecystectomy.

In our study, of the 303 patients with gallstones and abdominal symptoms who were not considered for cholecystectomy, 34% were o ered an alternative diagnosis or explanation for the symptoms. The alternative diagnoses were mainly functional gastrointestinal disorders, varying from acid re ux to obstipation. Management of these patients was left at the discretion of the attending physician and led to an equal health status and patient satisfaction over time in both study arms.

Based on this study, it might be argued that cholecystectomy is a mediocre solution for patients with symptoms that might be attributed to gallstones. But considering the di culty to de ne which criteria truly de ne the presence of symptomatic gallstones, it can be otherwise argued that having symptomatic gallstones is an over-rated diagnosis. Additionally, some studies have shown that cholecystectomy alone might also cause long-term metabolic changes in patients, including metabolic

syndrome and liver steatosis, and functional symptoms due to changes in pathways associated with bile acids.[35,36] Alternatively, gallstones might be an early hallmark of metabolic syndrome.[37] These findings should urge surgeons to rethink the pathophysiology of abdominal symptoms in patient candidates for cholecystectomy, and to manage expectations of the surgical approach. Symptomatic gallstones might be an epiphenomenon of another condition, for which cholecystectomy is not the solution. Further investigation is needed to determine how to best select patients who truly have gallbladder stones, which patients might benefit from cholecystectomy, and whether gallstones and functional gastrointestinal problems coincide. The Izbicki questionnaire used to assess the primary outcome in our study only assessed presence of abdominal pain, but no characteristics of pain. Future studies should also include characteristics of postoperative pain to conclude whether pain after cholecystectomy still includes biliary colics or is substituted with a different type of abdominal pain. Two such studies are currently underway in the Netherlands (NTR7267 and NTR7307) and could lead to an algorithm for the best management for patients with upper abdominal pain, other gastrointestinal symptoms, and gallstones.

Our large, nationwide, randomised trial included both academic and non-academic hospitals. The non-inferior design enabled assessment of the efficiency of a new treatment strategy (with fewer cholecystectomies), without the need for a superior result in treatment outcome. Our definition of being pain-free was based on an Izbicki Pain Score of 10 or less and a VAS of 4 or less, to ensure that only clinically relevant pain was indicated as persistent pain. When interpreting the results of this trial, a few limitations have to be taken into account. These include that around 30% of patients in the restrictive strategy were not treated per protocol. Most protocol deviations were in patients who underwent cholecystectomy without fulfilling the pre-specified criteria of the triage instrument for cholecystectomy; either the surgeon or the patient decided that cholecystectomy was the best therapeutic option despite the outcome of the triage instrument. Additionally, in the restrictive strategy, coincidentally more patients were included who had typical biliary symptoms according to the pre-specified criteria, than in the usual care arm. Therefore, the cohort of patients from the restrictive strategy contained a higher proportion of patients who were eligible for cholecystectomy compared with the cohort in the usual care arm. If this proportion had been equal in both arms, potentially even fewer cholecystectomies might have occurred in the restrictive strategy group compared with usual care. The number of cholecystectomies and gallstone-related complications might have also been affected by the short duration of follow-up; therefore we will follow up these patients for at least 5 years. Last, data for the duration of abdominal symptoms before randomisation and the interval between imaging and randomisation were not collected in this trial.

In summary, cholecystectomy offered partial relief of abdominal pain, because only 63% of patients were pain-free at 12 months. Although patients with typical biliary colics were pain-free more often after surgery, both a restrictive strategy including the internationally used Rome criteria and usual care were insufficient to select patients to achieve a pain-free state after cholecystectomy. Future research efforts should investigate improving the selection of gallstone patients who might have a high chance to benefit from cholecystectomy.

Contributors
PRdR, DB, GPW, JPHD, MGWD, MAB, and CJHMvL contributed to conception and design of the study. AHvD, SZW, CSSL, OB, SCD, QAJE, JH, KiʻtH, JJ, VBN, HMS, PS, HBACS, and DB contributed to acquisition of the data. AHvD, SZW, and MGWD had access to all the data and analysed the data. AHvD, SZW, PRdR, MGWD, and MAB contributed to interpretation of the data. AHvD and SZW drafted the manuscript, all other authors critically revised it. All authors approved the final version of the manuscript. The SECURE study principal investigators are (in alphabetical order): Marja A Boermeester, Marcel G W Dijkgraaf, Joost P H Drenth, Cornelius J H M van Laarhoven, and Philip R de Reuver. The principal investigators contributed equally to the supervision of the work.

Declaration of interests
We declare no competing interests.

Data sharing
The study protocol and statistical analysis plan are published online. To access de-identified participant data, contact Philip de Reuver (philip.dereuver@radboudumc.nl); access criteria will be defined after receipt of a research proposal.

For study protocol see https://bmcsurg.biomedcentral.com/articles/10.1186/s12893-016-0160-3

For statistical analysis plan see https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-018-2989-5

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References

1 Portincasa P, Moschetta A, Palasciano G. Cholesterol gallstone disease. Lancet 2006; 368: 230–39.
2 Shaffer EA. Gallstone disease: epidemiology of gallbladder stone disease. Best Pract Res Clin Gastroenterol 2006; 20: 981–96.
3 Lammert F, Gurusamy K, Ko CW, et al. Gallstones. Nat Rev Dis Primers 2016; 2: 16024.
4 The Rome Group for Epidemiology and Prevention of Cholelithiasis. The epidemiology of gallstone disease in Rome, Italy. Part I and II. Factors associated with the disease. Hepatology 1988; 8: 904–13.
5 Berger MY, van der Velden JJ, Lijmer JG, de Kort H, Prins A, Bohnen AM. Abdominal symptoms: do they predict gallstones? A systematic review. Scand J Gastroenterol 2000; 35: 70–76.
6 Dutch Society of Surgery. Evidence-based guideline. Diagnostic and treatment of gallstones. Utrecht: Dutch Society of Surgery, 2016.
7 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.
8 Society of American Gastrointestinal and Endoscopic Surgeons. Guidelines for the clinical application of laparoscopic biliary tract surgery. Los Angeles: SAGES, 2010.
9 Huntington CR, Cox TC, Blair LJ, et al. Nationwide variation in outcomes and cost of laparoscopic procedures. Surg Endosc 2016; 30: 934–46.

10 Lamberts MP, Lugtenberg M, Rovers MM, et al. Persistent and de novo symptoms after cholecystectomy: a systematic review of cholecystectomy effectiveness. *Surg Endosc* 2013; **27:** 709–18.

11 Wennmacker S, Lamberts M, Gerritsen J, et al. Consistency of patient-reported outcomes after cholecystectomy and their implications on current surgical practice: a prospective multicenter cohort study. *Surg Endosc* 2017; **31:** 215–24.

12 Thistle JL, Longstreth GF, Romero Y, et al. Factors that predict relief from upper abdominal pain after cholecystectomy. *Clin Gastroenterol Hepatol* 2011; **9:** 891–96.

13 Vetrhus M, Berhane T, Soreide O, Sondenaa K. Pain persists in many patients five years after removal of the gallbladder: observations from two randomized controlled trials of symptomatic, noncomplicated gallstone disease and acute cholecystitis. *J Gastrointest Surg* 2005; **9:** 826–31.

14 Wennmacker SZ, Dijkgraaf MGW, Westert GP, Drenth JPH, van Laarhoven C, de Reuver PR. Persistent abdominal pain after laparoscopic cholecystectomy is associated with increased healthcare consumption and sick leave. *Surgery* 2018; **163:** 661–66.

15 van Dijk AH, de Reuver PR, Besselink MGH. Assessment of available evidence in the management of gallbladder and bile duct stones: a systematic review of international guidelines. *HPB (Oxford)* 2017; **19:** 4.

16 Wennberg JE. Time to tackle unwarranted variations in practice. *BMJ* 2011; **342:** d1513.

17 Healthcare Insurances Netherlands. Practice variation report on 7 elective care diagnosis. Healthcare Insurances Netherlands (Zorgverkeraars Nederland), 2014. https://docplayer.nl/2496605-Praktijkvariatierapport-7-aandoeningen-electieve-zorg-2014.html (accessed Jan 31, 2016).

18 UK National Health Service (NHS). NHS atlas of variation in healthcare. 2011. www.england.nhs.uk/rightcare/products/atlas/ (accessed Dec 1, 2018).

19 The Dartmouth Institute for Policy & Clinical Practice. The Dartmouth atlas. www.dartmouthatlas.org (accessed Dec 1, 2018).

20 Birkmeyer JD, Reames BN, McCulloch P, Carr AJ, Campbell WB, Wennberg JE. Understanding of regional variation in the use of surgery. *Lancet* 2013; **382:** 1121–29.

21 Malhotra A, Maughan D, Ansell J, et al. Choosing wisely in the UK: the Academy of Medical Royal Colleges' initiative to reduce the harms of too much medicine. *BMJ* 2015; **350:** h2308.

22 Morden NE, Colla CH, Sequist TD, Rosenthal MB. Choosing wisely – the politics and economics of labeling low-value services. *N Engl J Med* 2014; **370:** 589–92.

23 de Reuver PR, van Dijk AH, Wennmacker SZ, et al. A randomized controlled trial to compare a restrictive strategy to usual care for the effectiveness of cholecystectomy in patients with symptomatic gallstones (SECURE trial protocol). *BMC Surg* 2016; **16:** 46.

24 Wennmacker SZ, van Dijk AH, Drenth JPH, et al. Statistical analysis plan of a randomized controlled trial to compare a restrictive strategy to usual care for the effectiveness of cholecystectomy (SECURE trial). *Trials* 2018; **19:** 604.

25 Lee YS, Kang BK, Hwang IK, Kim J, Hwang JH. Long-term outcomes of symptomatic gallbladder sludge. *J Clin Gastroenterol* 2015; **49:** 594–98.

26 Keizman D, Ish-Shalom M, Konikoff FM. The clinical significance of bile duct sludge: is it different from bile duct stones? *Surg Endosc* 2007; **21:** 769–73.

27 Berger MY, Olde Hartman TC, van der Velden JJ, Bohnen AM. Is biliary pain exclusively related to gallbladder stones? A controlled prospective study. *Br J Gen Pract* 2004; **54:** 574–79.

28 Brooks R. EuroQol: the current state of play. *Health Policy* 1996; **37:** 53–72.

29 Bloechle C, Izbicki JR, Knoefel WT, Kuechler T, Broelsch CE. Quality of life in chronic pancreatitis–results after duodenum-preserving resection of the head of the pancreas. *Pancreas* 1995; **11:** 77–85.

30 Eypasch E, Williams JI, Wood-Dauphinee S, et al. Gastrointestinal Quality of Life Index: development, validation and application of a new instrument. *Br J Surg* 1995; **82:** 216–22.

31 Nieveen Van Dijkum EJ, Terwee CB, Oosterveld P, Van Der Meulen JH, Gouma DJ, De Haes JC. Validation of the gastrointestinal quality of life index for patients with potentially operable periampullary carcinoma. *Br J Surg* 2000; **87:** 110–15.

32 Vetrhus M, Soreide O, Eide GE, Solhaug JH, Nesvik I, Sondenaa K. Pain and quality of life in patients with symptomatic, non-complicated gallbladder stones: results of a randomized controlled trial. *Scand J Gastroenterol* 2004; **39:** 270–76.

33 Lamberts MP, Den Oudsten BL, Gerritsen JJ, et al. Prospective multicentre cohort study of patient-reported outcomes after cholecystectomy for uncomplicated symptomatic cholecystolithiasis. *Br J Surg* 2015; **102:** 1402–09.

34 Mertens MC, Roukema JA, Scholtes VP, De Vries J. Risk assessment in cholelithiasis: is cholecystectomy always to be preferred? *J Gastrointest Surg* 2010; **14:** 1271–79.

35 Di Ciaula A, Garruti G, Wang DQ, Portincasa P. Cholecystectomy and risk of metabolic syndrome. *Eur J Intern Med* 2018; **53:** 3–11.

36 Uyanikoglu A, Akyuz F, Ermis F, et al. Does cholecystectomy increase the esophageal alkaline reflux? Evaluation by impedance-pH technique. *J Neurogastroenterol Motil* 2012; **18:** 187–93.

37 Chen LY, Qiao QH, Zhang SC, Chen YH, Chao GQ, Fang LZ. Metabolic syndrome and gallstone disease. *World J Gastroenterol* 2012; **18:** 4215–20.