# Is biliary pain exclusively related to gallbladder stones? A controlled prospective study

Marjolein Y Berger, Tim C olde Hartman, Jurgen J I M van der Velden and Arthur M Bohnen

*SUMMARY*

***Background:*** *The uncertainty around true clinical manifestations of gallbladder stone disease is in contrast with the unanimous recommendation that only symptomatic gallstones should be treated.*

***Aim:*** *To evaluate the relationship between biliary pain, other gastrointestinal symptoms and gallstones.*

***Design of study:*** *A pragmatic, prospective cohort questionnaire study.*

***Setting:*** *Seventy-five general practices in Rotterdam, The Netherlands.*

***Method:*** *All patients suspected by their general practitioner (GP) to have gallstone disease underwent ultrasound examination of the upper abdomen. Using a self-administered questionnaire, the presence of 11 gastrointestinal symptoms was assessed at inclusion and after 1 year. Likelihood ratios (LRs) for the presence of gallstones and symptom relief rates after 1 year were calculated. The mean difference in health status at inclusion and after follow-up was calculated for patients without gallstones, for patients with gallstones who were operated on and for patients with gallstones who were not operated on.*

***Results:*** *In total, 61% of the patients with gallstones diagnosed by ultrasound scan reported biliary pain, as did 45% of the patients without gallstones (LR = 1.34, 95% confidence interval [CI] = 1.05 to 1.71). Patients operated on for gallstone disease did not show significant relief of biliary pain compared to patients not operated on for gallstones or patients without gallstones (87%, 63% and 83%, respectively). Health status improved in all patients. The mean improvement in health status did not differ between the three patient groups. GPs were able to discriminate between patients with high and low probability of gallbladder stones by ultrasound examination (53% versus 23%). This selection, however, did not predict the outcome of cholecystectomy.*

***Conclusion:*** *Neither biliary pain nor any other gastrointestinal symptom was consistently related to gallstone disease. Therefore, the indication for elective cholecystectomy cannot be based on the presence of biliary pain alone. Relief of biliary pain in patients operated on for gallstones should not simply be attributed to a successful cholecystectomy.*

***Keywords:*** *cholecystectomy, laparoscopic; cholelithiasis; prognosis; prospective studies; signs and symptoms.*

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Submitted: 27 January 2003; Editor's response: 3 June 2003; final acceptance: 24 February 2004.



## Introduction

THE term 'symptomatic gallstones' is widely used and implies that the symptoms specifically caused by gallstones are known. A wide range of gastrointestinal symptoms have been attributed to gallstones, but a causal relationship with gallstones has not yet been established.

A clinical suspicion of gallstones arises when a patient presents with so-called 'biliary pain'. In the Roma88 working team report, biliary pain was arbitrarily defined as 'a severe steady pain, lasting more than 15–30 minutes, usually located in the epigastrium and/or right upper quadrant, and sometimes radiating to the back'.[1] In their guidelines for the treatment of gallstones, the American College of Physicians followed Ransohoff and Gracie in their definition that biliary pain occurs suddenly as severe steady pain that is unaffected by household remedies, position change or the passage of gas.[2,3] These definitions are mainly based on retrospective or prospective descriptions of abdominal symptoms in patients with gallstones without the use of a control group. Prevalence studies comparing the presence of biliary pain in patients with and without gallstones have found contradictory results about the association between biliary pain and gallstones.[4]

The assumption has often been that if gallstones are found in symptomatic patients then gallstones are the cause of the symptoms and referral for cholecystectomy is indicated. However, whereas both gallstones and abdominal symptoms, including pain, are common in adults,[5] the occurrence of both might be due to chance alone. This may explain why 6–27% of patients with biliary pain did not obtain relief of biliary pain after cholecystectomy.[6,7]

To allow for a valid evaluation of treatment effectiveness, symptom relief rates should be compared between patients operated on for gallbladder stone disease and a comparable control group with identical follow-up. We designed a pragmatic cohort study of patients in whom the general practitioner (GP) suspected symptomatic gallstones. The aim was to establish whether biliary pain was the only symptom in patients operated on for symptomatic gallstones and whether patients who proved not to have gallstones, following ultrasound examination, suffered from biliary pain. After a 1-year follow-up, relief rates for biliary pain were compared in three patient groups: patients without gallbladder stones, patients operated on for gallbladder stone disease, and patients with gallbladder stones who were not operated on.

## Method

### *Patients*

Seventy-five GPs in Rotterdam, in The Netherlands, participated in the study. All consecutive patients with upper

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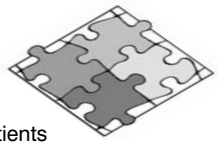

*What do we know?*

Prevalence studies comparing the presence of abdominal symptoms in patients with and without gallstones found contradictory results about the association between biliary pain and gallstones.

*What does this paper add?*

Gallbladder stones do not exclusively cause biliary pain, and this makes it difficult to select patients for cholecystectomy based on this symptom alone. Well designed randomised controlled trials are urgently needed to clarify the indication for elective cholecystectomy and to evaluate its effect.

abdominal pain aged 18 years and older who consulted a participating GP between January 1996 and June 1998, and in whom the GP suspected symptomatic gallbladder stones, were eligible for the study. After obtaining written informed consent, patients were referred to a GP diagnostic service or, in the case of high suspicion of symptomatic gallbladder stones, to the radiology department of one of nine local hospitals for an ultrasound examination of the upper abdomen. Subsequent referral to a surgeon for cholecystectomy was decided on by the GP. All patients with gallbladder stones were preoperatively examined by a surgeon, who indicated further diagnostic investigation, i.e. liver function tests in all patients, and endoscopic examination or barium enema examination whenever applicable. Patients with acute cholecystitis or cholangitis, and patients with bile duct stones (based on the presence of jaundice and the results of liver function tests), were excluded. The surgeon gave the final indication for cholecystectomy. The research ethics committee of the University Hospital Rotterdam approved the study protocol.

### *Assessments*

At inclusion, just before ultrasound examination, the patients were given a structured self-administered questionnaire to complete about the presence or absence of 11 symptoms during the previous month. The questionnaire had been used and validated in a previous randomised controlled trial.[8] The symptoms were: biliary pain (defined as: acute, steady, severe or very severe, and upper abdominal pain lasting 1 hour or more),[3] upper abdominal pain, upper abdominal pain after fatty food intake, vomiting, nausea, feeling of distension (bloating), belching, acid regurgitation, constipation, diarrhoea, and flatulence. Patients were asked to mark their health status on a visual analogue scale from 0–100. The radiologist was blinded to the answers in the questionnaire.

One year after inclusion, all patients were sent a copy of the same questionnaire by post. Non-responders received a reminder by post and a second reminder by telephone. A structured questionnaire was posted to participating GPs. In this questionnaire the GP was asked about other diagnoses for the initial symptoms of the patients, whether patients had consulted the GP during the 1-year follow-up with symptoms similar to those at inclusion, and whether bile duct stones were detected after cholecystectomy.

Ultrasound examinations were performed by radiologists, senior radiological residents or experienced radiology technicians. All patients were examined in a fasting state with a 3.5 MHz scanner according to a standardised protocol.

### *Statistical analysis*

Likelihood ratios with 95% confidence intervals (CIs) were calculated to estimate the value of gastrointestinal symptoms for discrimination between patients with and without gallbladder stones.

Symptom relief rates after 1-year follow-up were calculated for each symptom. The relief rate was defined as the number of patients in which the symptom had disappeared after 1 year divided by the number of patients exhibiting the symptom at inclusion. Differences in proportions were tested with a $\chi^2$ test statistic. Differences between means for different groups were tested using a one-way analysis of variance (ANOVA) or a Kruskall–Wallis test where appropriate.

To evaluate the relationship between patient characteristics and relief of upper abdominal pain, a multivariable logistic regression analysis was performed, with the relief rate for upper abdominal pain as the dependent variable. Patient characteristics, group status (without gallbladder stones, with gallbladder stones but not operated on, or with gallbladder stones and operated on), and level of suspicion for the presence of gallbladder stones were entered as independent variables. For each of the independent variables, adjusted odds ratios (ORs) with asymptomatic 95% CIs were calculated from the regression coefficients. SPSS software was used to perform the analyses.

## Results

A total of 233 patients were included in the study. Of these, 107 (46%) patients were found to have gallbladder stones on ultrasound examination and 85 patients underwent an elective cholecystectomy. A total of 213 (91%) patients responded to the postal questionnaire after 1 year (Figure 1). Of the 20 non-responders, one patient had died of a hepatocellular carcinoma, five patients had moved to an unknown address, and for 14 patients the reason for non-response was unknown. Non-responders did not differ from the responding patients with regard to age, sex and the severity of upper abdominal pain.

Of the 107 patients with gallstones, 22 were not operated on for the following reasons: the surgeon decided that the complaints in two patients were not related to gallstones; in seven patients the GP decided not to refer for cholecystectomy because of atypical complaints; 11 patients refused surgery; and the reasons for not operating on two patients were unknown.

There were significant differences between the three groups. The highest mean age (54 years; $P = 0.03$) was found in the patients with gallstones who were not operated on. Patients without gallstones used more $H_2$-receptor antagonists at inclusion compared with patients with gallstones who were and were not operated on (25% versus 9% and 14%, $P = 0.011$). Sex distribution ($P = 0.094$), and proportion of patients with comorbidity ($P = 0.479$), showed no significant differences between the three groups (Table 1).

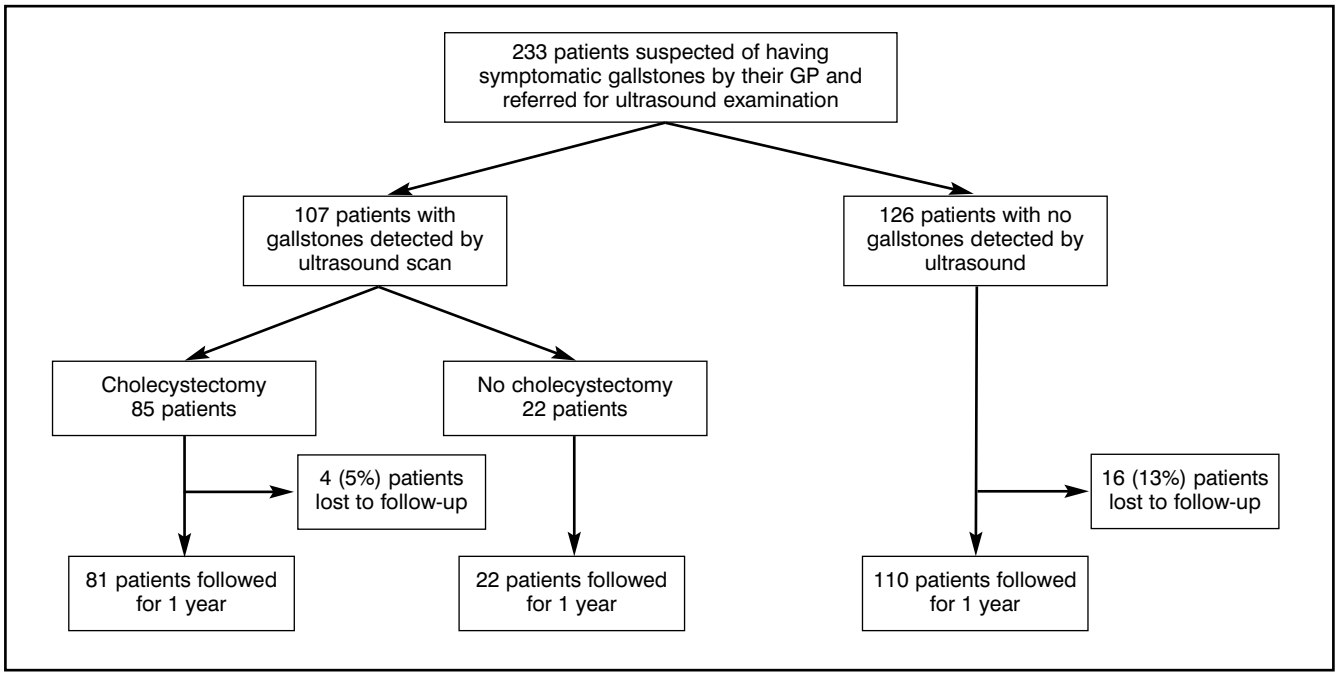


*Figure 1. Flow chart of inclusion and follow-up of patients.*

GPs selected patients who were highly suspected of having gallstones. In patients who had been operated on the proportion of patients at a high level of suspicion was largest (94%, $P = 0.0001$) (Table 1).

Gallstones were found by ultrasound examination in more patients at a high level than at a low level of suspicion (53% versus 23%, $P = 0.0001$). At inclusion, these patients reported more biliary pain, upper abdominal pain and vomiting (Table 2).

At inclusion, health status was comparable between the three groups ($P = 0.528$), and health status improved in all three patient groups after follow-up. The mean difference between inclusion and follow-up was comparable ($P = 0.997$) (Table 3).

In the multivariable logistic regression analysis, the presence of comorbidity was related to a higher relief rate for upper abdominal pain (OR = 2.8, 95% CI = 1.33 to 5.96), and this relationship was found in all three patient groups. In

*Table 1. Patient characteristics.*

| | Patients without gallstones ($n = 126$) | Patients with gallstones who were not operated on ($n = 22$) | Patients with gallstones who were operated on ($n = 85$) |
|---|---|---|---|
| Mean age in years (range) | 47.7 (21–81) | 54.0 (34–71) | 43.6 (17–79) |
| Number of women (%) | 90 (71) | 15 (68) | 71 (84) |
| Number of patients using $H_2$-receptor antagonist at inclusion (%) | 32 (25) | 3 (14) | 8 (9) |
| Number with comorbidity (%) | 41 (33) | 9 (41) | 34 (40) |
| Number of patients at a high level of suspicion for the presence of gallstone disease (%) | 83 (66) | 14 (64) | 80 (94) |
| Mean number of months to follow-up (range) | 15.2 (3–33) | 19.2 (9–30) | 18.7 (2–40) |

*Table 2. Frequency of symptoms related to gallstones at inclusion in patients at a low level of suspicion (*n *= 56) and at a high level of suspicion (*n *= 177) for gallbladder stone disease.*

| | Low level of suspicion (%) | High level of suspicion (%) | *P*-value[a] |
|---|---|---|---|
| Biliary pain | 21/56 (38) | 101/177 (57) | 0.011 |
| Upper abdominal pain | 34/56 (61) | 144/177 (81) | 0.002 |
| Vomiting | 12/54 (22) | 67/172 (39) | 0.024 |
| Gallstones detected by ultrasound scan | 13/56 (23) | 94/177 (53) | 0.0001 |

[a]$\chi^2$ test, 1 degree of freedom.

*Table 3. Health status at inclusion and after follow-up.*

| | Patients without gallstones (*n* = 126) | Patients with gallstones who were not operated on (*n* = 22) | Patients with gallstones who were operated on (*n* = 85) |
|---|---|---|---|
| Mean health status score (0–100) at inclusion (SD) | 59.6 (22.9) | 63.2 (16.4) | 63.0 (21.3) |
| Mean health status score (0–100) after follow-up (SD) | 74.9 (16.9) | 81.7 (15.6) | 77.2 (18.8) |
| Mean difference in health status (95% CI) | 15.3 (8.9 to 21.6) | 15.8 (4.3 to 27.2) | 16.3 (9.8 to 22.7) |

SD = standard deviation.

*Table 4. Frequency of symptoms at inclusion in patients without gallstones (*n *= 126), patients with gallstones who were not operated on (*n *= 22) and patients who were operated on for gallstones (*n *= 85).*

| | Patients without gallstones (%)[a] | Patients with gallstones who were not operated on (%)[a] | Patients with gallstones who were operated on (%)[a] | *P*-value[b] | Likelihood ratio for gallstones given symptom is present (% [95% CI]) |
|---|---|---|---|---|---|
| Biliary pain | 57/126 (45) | 10/22 (46) | 55/85 (65) | 0.017 | 1.34 (1.05 to 1.71) |
| Upper abdominal pain | 97/126 (77) | 16/22 (73) | 77/85 (91) | 0.024 | 1.13 (0.99 to 1.29) |
| Upper abdominal pain after fatty food intake | 55/126 (44) | 9/22 (41) | 53/85 (62) | 0.019 | 1.33 (1.01 to 1.74) |
| Vomiting | 31/122 (25) | 5/21 (24) | 43/83 (52) | 0.0001 | 1.82 (1.25 to 2.63) |
| Dyspeptic symptoms | | | | | |
| Nausea | 82/126 (65) | 16/22 (73) | 67/83 (81) | 0.05 | 1.21 (1.02 to 1.45) |
| Belching | 83/124 (67) | 83/124 (67) | 64/84 (76) | 0.35 | 1.11 (0.95 to 1.31) |
| Bloating | 87/123 (71) | 14/22 (64) | 67/85 (80) | 0.20 | 1.07 (0.90 to 1.27) |
| Acid regurgitation | 63/125 (50) | 7/22 (32) | 45/85 (53) | 0.20 | 0.96 (0.73 to 1.27) |
| Diarrhoea | 50/126 (40) | 11/22 (50) | 34/85 (40) | 0.65 | 1.06 (0.80 to 1.40) |
| Constipation | 49/125 (39) | 5/21 (24) | 31/84 (37) | 0.40 | 0.87 (0.60 to 1.27) |
| Flatulence | 91/126 (72) | 17/22 (77) | 55/85 (65) | 0.37 | 0.93 (0.79 to 1.10) |
| Three or more symptoms | 84/121 (69) | 17/22 (77) | 69/82 (84) | 0.06 | - |

[a]Not all patients answered all questions. [b]$\chi^2$ test, 2 degrees of freedom.

*Table 5. Rate of relief of symptoms after 1 year in patients without gallstones (*n *= 110), patients with gallstones who were not operated on (n = 22) and patients operated on for gallstones (*n *= 81).*

| | Relief in patients without gallstones (%)[a] | Relief in patients with gallstones who were not operated on (%)[a] | Relief in patients with gallstones who were operated on (%)[a] | *P*-value[b] |
|---|---|---|---|---|
| Biliary pain | 40/48 (83) | 5/8 (63) | 45/52 (87) | 0.24 |
| Upper abdominal pain | 48/79 (61) | 7/12 (58) | 37/41 (70) | 0.41 |
| Upper abdominal pain after fatty food intake | 27/42 (64) | 5/7 (71) | 34/51 (67) | 0.92 |

[a]Not all patients answered all questions. [b]$\chi^2$ test, 2 degrees of freedom.

total, 36% of patients reported concomitant cardiac disease, gastric disease (i.e. reflux oesophagitis, gastritis), and abdominal disease (i.e. irritable bowel syndrome).

### *Symptoms at baseline and relief rates after 1-year follow-up*

Tables 4 and 5 give the frequency of symptoms at inclusion and the symptom relief rates after 1 year for the three groups.

At inclusion, patients who were operated on reported biliary pain significantly more often than patients without gallstones and patients with gallstones who were not operated on (65% versus 45% and 46%, respectively, $P = 0.017$) (Table 4). After 1-year follow-up, however, there was no significant difference in the relief rate of biliary pain between the three patient groups (87%, 83% and 63%, respectively, $P = 0.24$). Also, upper abdominal pain and upper abdominal pain after fatty food intake were reported more often at inclusion by operated patients, but after 1 year the relief rates for these symptoms were comparable between the three groups (Table 4 and 5).

Of the dyspeptic symptoms, only nausea was reported more often in patients who had been operated on compared

with patients without gallstones and patients with gallstones who had not been operated on (81% versus 65% and 73%, respectively, $P = 0.05$). Of the patients who were operated on, 84% reported three or more dyspeptic symptoms at inclusion; this was comparable to the rates in the other two groups (69% and 77%, $P = 0.06$) (Table 4).

### *GP questionnaire*

Eleven (15%) GPs did not respond to the follow-up questionnaire. In total, 24 (33%) patients who had been operated on visited their GP with symptoms similar to those before cholecystectomy. The presence of common bile duct stones was not evaluated in any of these patients. In two of these patients a duodenal ulcer was diagnosed, and in one the GP diagnosed functional gastritis.

In the patients without gallstones, 69 (63%) consultations for symptoms similar to those at inclusion resulted in a further diagnosis in 35 patients. Gastritis was diagnosed in 17 patients (this was functional in 12, due to alcohol abuse in three, *Helicobacter pylori* in one, and viral in one), irritable bowel syndrome in seven patients, and gastro-oesophageal reflux in five. In three patients, other diagnoses were made and in three further patients, the GP reconsidered the diagnosis of cholelithiasis because of the presence of sludge in the gallbladder on ultrasound scanning.

## Discussion

### *Summary of main findings*

We have described 233 patients in whom their GPs suspected gallstone disease. In total, 65% of the patients with gallstones who were operated on reported biliary pain at inclusion, as did 46% of the patients with gallstones who were not operated on and 45% of patients who did not have gallstones. Relief rates for biliary pain after 1 year were comparable in the three patient groups. These findings indicate that gallstones do not exclusively cause severe, steady, upper abdominal pain, nor can symptom relief exclusively be attributed to gallstone removal.

The burden of dyspeptic symptoms in all patients was high; 77% of all patients reported three or more dyspeptic symptoms. Of the patients who were operated on, 84% reported three or more dyspeptic symptoms. None of the gastrointestinal symptoms allowed clinically relevant discrimination between patients with and without gallbladder stones. Likelihood ratios for the presence of gallbladder stones were all close to 1. In contrast, GPs were able to select patients at risk from gallstones for ultrasound examination. A high suspicion for symptomatic gallbladder stones, however, did not predict relief of upper abdominal pain after cholecystectomy.

### *Comparison with other studies*

A clinical suspicion of gallstones arises when a patient presents with so-called 'biliary pain'. In all definitions of biliary pain the sudden occurrence and severity of the pain were important characteristics. Our definition of biliary pain has underlined these characteristics.

In a systematic literature review biliary pain was consistently related to the presence of gallbladder stones[4]; however, only 20% of patients with suspected gallbladder stone disease presented with biliary pain. In this study, 35% of the patients who went on to have surgery did not initially report biliary pain according to a widely accepted definition. However, 91% of the patients with gallstones in this study who were operated on did report upper abdominal pain. These findings suggest that either the definition of biliary pain should be adjusted or that the indication for surgery is not always adequate.

### *Strength and limitations of the study*

Only a few studies have used a control group in the evaluation of postoperative symptoms in gallstone disease.[9-11] In these control groups the frequency of symptoms was assessed at one point in time, either retrospectively or in cross section. Subjects in these control groups were either patients suffering from other non-related diseases or healthy volunteers. To our knowledge, no study has prospectively followed a control group when evaluating gastrointestinal symptoms before and after cholecystectomy.

In the present study, patients with and without gallbladder stones consulted their GP with symptoms that caused the GP to suspect symptomatic gallbladder stones. Both groups were followed for a comparable period of time, yet it can be successfully argued that the patients without gallbladder stones are not comparable with patients after cholecystectomy. In addition, the third group of patients with gallbladder stones who had not been operated on was not a perfect control group; in 50% of these patients the reason not to operate was 'doubt about the relation between symptoms and gallbladder stones'. Although the three patient groups differed significantly, only the presence of comorbidity could be related to a higher relief of upper abdominal pain. A total of 36% of the patients had concomitant cardiac disease, gastric disease (i.e. reflux oesophagitis, gastritis), or other gastrointestinal disease (i.e. irritable bowel syndrome): all these diseases can cause upper abdominal pain. Exclusion of these diseases as a cause of upper abdominal pain before diagnosing symptomatic gallbladder stones may optimise the indication for cholecystectomy and thereby explain the better outcome in patients who had been operated on.

The best control group would have been a group of patients with gallstones randomly selected not to have cholecystectomy; such a study was recently performed.[12] In patients with uncomplicated symptomatic gallbladder stone disease, cholecystectomy was compared with 'watchful waiting'. After a median follow-up of 67 months, gallstone-related complications were less in the watchful-waiting arm compared with postoperative complications in the cholecystectomy arm. In total, 17% of patients in the watchful-waiting arm were referred again because of upper abdominal pain. Relief of symptoms, however, was not systematically assessed in this trial. The authors concluded that expectant management carries a low risk of complications and should be considered for all patients with uncomplicated gallbladder stone disease. Our findings that relief of biliary pain and upper abdominal pain were comparable in the three patient groups suggest that relief of symptoms in patients who have been operated on cannot exclusively be attributed to cholecystectomy. This supports the idea that having the gallbladder removed in the case of upper abdominal pain

coinciding with the presence of gallbladder stones may rest on common practice rather than on evidence-based medicine.

### *Implications for future research and policy*

Well designed randomised controlled trials are urgently needed to clarify the indication for elective cholecystectomy. GPs should be aware that, even in the presence of gallbladder stones, biliary pain cannot be attributed exclusively to gallbladder stone disease. Before a diagnosis of symptomatic gallbladder stones is made, other pathology common in general practice; for example, reflux oesophagitis and irritable bowel syndrome, should be excluded.

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### Acknowledgements

The authors would like to thank the 75 general practitioners in the Rotterdam district, the departments of radiology and surgery of the following hospitals: the University Hospital Rotterdam, Havenziekenhuis, Holyziekenhuis, Schielandziekenhuis, St Clara Ziekenhuis, St. Franciscus Gasthuis, IJssellandziekenhuis, Ikazia Ziekenhuis, Zuiderziekenhuis, and the Stichting Trombosedienst en Artsenlaboratorium Rotterdam diagnostic service for GPs, for their cooperation in this study.