Can Laparoscopic Cholecystectomy Prevent Recurrent Idiopathic Acute Pancreatitis?

A Prospective Randomized Multicenter Trial

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Objective: The aim of the present trial was to ascertain whether laparoscopic cholecystectomy (LCC) can prevent recurrent attacks of idiopathic acute pancreatitis (IAP).

Summary: Up to 50% to 75% of IAP may be due to microlithiasis, which is undetectable by conventional imaging methods.

Methods: This randomized, prospective trial included 85 patients (39 in the LCC and 46 in the control group) in 8 hospitals in Finland. We included adult patients (over 18 years) with their first attack of IAP. The diagnosis of IAP was based on the exclusion of common etiological reasons for acute pancreatitis (AP), whereafter the patients were randomized into conservative watchful waiting (controls) or LCC group. The primary end point was the number of patients with recurrent AP during the follow-up. All recurrent attacks of AP after an initial IAP episode were registered.

Results: During a median follow-up of 36 (5–58) months, the recurrence of IAP was significantly higher in the control group than in LCC group (14/46 vs. 4/39, $P = 0.016$), as was also the number of recurrences (23/46 vs. 8/39, $P = 0.003$). In the subgroup of patients with at least 24 months' follow-up, the recurrence was still higher among controls (14/37 vs. 4/35, $P = 0.008$). In patients with normal liver function, recurrence was also significantly higher in the control than in the LCC group (13/46 vs. 4/39, $P = 0.026$). During surgery, 23/39 (59%) of the gallbladders were found to contain biliary stones or sludge.

Conclusions: LCC can effectively prevent the recurrence of IAP when all other possible etiologies of pancreatitis are carefully excluded. A total of 5 patients needed to be treated (NNT-value) to prevent 1 IAP.

Keywords: acute pancreatitis, laparoscopic cholecystectomy, lipid-lowering drugs, microlithiasis

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Alcohol and gallstones are the most common etiological factors in acute pancreatitis (AP) in the majority of Western countries.[1,2] In Finland, the incidence of AP has been constantly increasing concomitant with increasing alcohol consumption.[3] Other, more rare, etiological factors for AP are tumors, endoscopic retrograde cholangiopancreatography (ERCP), hyperlipidemia, surgery, hypercalcemia, medication, and some autoimmune disorders.[4,5] Also, some gene mutations may predispose to recurrent AP.[4,6] Despite careful diagnostic and etiologic work-up of AP, some 10% to 30% of cases remain unexplained and are called idiopathic acute pancreatitis (IAP).[4]

It has been suggested that as many as 50% to 75% of IAP cases may be due to microlithiasis.[7,8] Small biliary stones in less than 3 mm diameter cannot always be detected by conventional transabdominal ultrasound (US) and they may lead to recurrences and even to chronic pancreatitis.[8] The reason for recurrence in some patients primarily suspected of having alcohol-induced recurrent episodes, may in fact be gallstones or microlithiasis.[9–12] When transabdominal US is negative, endoscopic ultrasonography (EUS) in skilful hands has been shown to detect microlithiasis in approximately 90% of cases.[13–15] The problem is, however, that skillful EUS is currently unavailable in many hospitals worldwide.

In the context of microlithiasis as an etiological factor for IAP, various treatment modalities, such as ursodeoxycholic acid treatment, ERCP (sphincterotomy and/or stenting), or laparoscopic cholecystectomy (LCC) have been proposed.[16–19] In a study by Ros et al,[19] cholecystectomy prevented 17 out of 18 relapses during a 36-month follow-up period, suggesting the superiority of this method. Prospective, randomized studies on the impact of empiric cholecystectomy in preventing recurrent episodes of IAP are lacking. The hypothesis and primary aim of the present randomized trial was to evaluate whether empiric cholecystectomy could prevent recurrent attacks of AP after an initial IAP.

PATIENTS AND METHODS

Trial Design

This randomized, prospective, parallel, superiority trial included 85 patients (39 in the LCC and 46 in the control group) in 8 hospitals in Finland. The trial was conducted between January 2009 and January 2013. This trial aimed to prove that LCC can prevent recurrent attacks of IAP. Allocation ratio to operative versus conservative treatment was 1:1.

Changes to Trial Design

Our original trial plan was to include all 154 patients based on the power calculation (see below). Interim analysis after 4 years was performed to evaluate safety of watchful waiting. The trial was

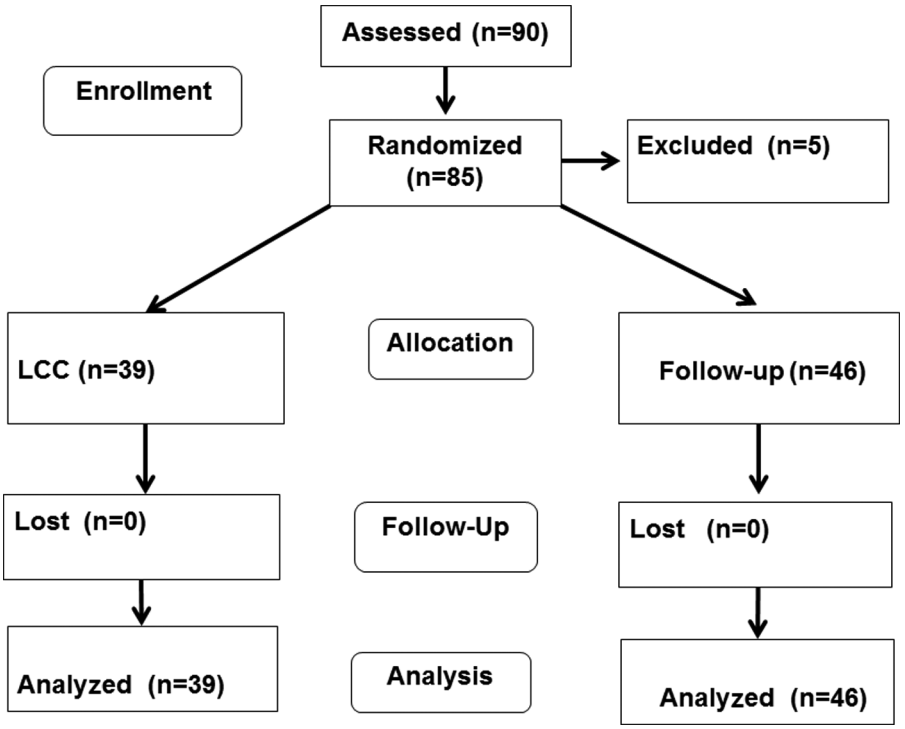

FIGURE 1. Flow chart of the trial.

terminated because the interim analysis strongly supported our primary aim that LCC reduces recurrences of IAP ($P < 0.016$). Hence, only 90 patients with IAP (43 in the LCC and 47 in the control group), instead of the originally intended 154, were enrolled for the trial. The trial flow chart is shown in Figure 1.

Participants and Eligibility Criteria

Recruitment was carried out in the gastroenterological and surgical departments of 8 Finnish hospitals (4 university and 4 central hospitals) enrolling patients with IAP.

We included adult patients (over 18 years) with their first attack of IAP and whose diagnosis of AP was based on the typical clinical picture (belt-like upper abdominal pain), serum amylase level more than 3 times over the upper normal range, and imaging findings suggesting AP. The included patients were carefully examined and the diagnosis of IAP was confirmed by exclusion of all known etiological factors for AP.

The initial diagnostic work-up of AP (laboratory tests, imaging) was done in each hospital during the hospital stay. In patients needing further examinations such as MRCP or gene tests, the recruitment was undertaken after these examinations at an extra outpatient visit. Medication, disease history, and family history were carefully recorded. Abuse of alcohol as an underlying reason for AP was excluded using the Alcohol Use Disorders Identification Test (AUDIT),[20] with scores of 8 points or less being considered normal. Conventional transabdominal US was undertaken in both the acute phase of pancreatitis and after recovery as an outpatient examination to detect possible gallstones. Laboratory tests were run to detect possible alcohol abuse [desialotransferrine (CDT) and glutamyltransferase (GT)], biliary disease [alkaline aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phoshatase (ALP), bilirubin (BIL)], or other etiologies such as hyperlipidemia [triglycerides (TRIGLY)] and hypercalcemia [calcium (S-CA)]. Patients with elevated liver function test results, but no gallstones in US, underwent MRCP to exclude the possibility of bile duct stones. SPINK-1 and PRSS-1 mutations were searched in patients whose relatives had previously had AP. EUS was not performed since it was not available in all hospitals of the trial. Other imaging modalities such as computed tomography (CT) were used whenever clinically indicated, not only for the etiology but for the severity of the AP episode.[21]

Patients who had previously undergone cholecystectomy were excluded. Patients with chronic pancreatitis or abuse of alcohol were also excluded, likewise those unwilling to undergo LCC. Scoring over 8 points on AUDIT, gallbladder, or bile duct stones detected by any imaging methods were excluded. In 2 cases a genetic disorder was suspected. Test results above were negative and the patients were not excluded. Genetic testing of cystic fibrosis transmembrane regulator (CFTR) mutations was not included in the protocol, since they are extremely rare in Finland (never detected in adults).

All removed gall bladders were evaluated both by the surgeon and the pathologist, and special attention was paid to possible small stones. The biliary stones or sludge were assessed visually without microscopical examination of bile from the surgically removed gallbladders.

The prophylactic role of statins in the prevention of biliary microlithiasis is not known.

The possible association of IAP with the use of statins and other lipid lowering drugs was therefore monitored. These drugs may be associated with a decreased risk for gallstones and biliary-induced AP.[22–24] To investigate the possible role of lipid-lowering drugs in IAP, all lipid-lowering drugs, including statins (simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, and rosuvastatin), fibrates (fenofibrate, gemfibrozil), and ezetimibe with daily doses, were also recorded.

Interventions

In the LCC group, the standard four-port technique of LCC was used. LCC was performed as a retrograde technique, in which the

dissection begins at the gallbladder-cystic duct junction towards the fundus. Titanium clips were always used for occlusion of the cystic duct and the artery. For diagnosing postoperative complications, ultrasound, computerized tomography, and magnetic resonance imaging modalities were available.

In the watchful waiting group, the patients were followed without surgical intervention. Recurrent attacks of IAP were assessed from hospital records and by telephone calls every 6 months and all episodes of AP were recorded. The criteria for recurrent AP were the same as for the first AP.

Outcomes

Primary outcome of this randomized multicenter trial was the number of patients with recurrent AP during the follow-up. Secondary outcome was the number of recurrent attacks during the follow-up. Also, the use of statins as a possible co-factor was recorded.

Sample Size

According to the initial power calculation, 77 subjects per treatment group were needed for the trial to achieve a statistical power of 0.90 with an α of 0.05 (2-tailed). The calculation assumed that the recurrence rate of IAP would be 25% in the LCC group and 50% in the control group. This was based on the assumption that about half of the IAP would be of microlithiasis and their recurrence might be prevented.[7] However, interim analysis confirmed that our primary hypothesis was strongly supported with smaller patient groups and shorter follow-up, and we therefore discontinued patient enrollment.

Randomization and Ethics

Randomization was performed using sequentially numbered and sealed envelopes, which were opened in each center of the trial. We used block randomization in each center (n = 10). The consequent patients with the diagnosis of IAP were included the trial, if possible. Every hospital evaluated their IAP patients separately by the study nurses and surgeons who also enrolled and assigned participants to this trial. The person enrolling participants did not know in advance which treatment the next person would get. A study nurse opened the sealed envelopes to avoid selection bias. Recurrent attacks of IAP were assessed separately in each hospital by the study nurse/surgeon.

Patients fulfilling the diagnostic criteria for IAP received written and oral information on the aims and content of the trial in accordance with the Helsinki Declaration. The respective ethics committees in the hospitals approved the trial protocol and the protocol was entered in the clinicaltrial.gov registry (NCT00784355). All trial patients signed the consent forms.

Statistics

Data were analyzed using IBM SPSS Statistics 20.0 (IBM Corp., Armonk, NY). Statistical analysis was performed using Fisher exact test, Mann-Whitney *U* test and logistic regression analysis. *P*-values less than 0.05 were considered statistically significant.

RESULTS

Participant Flow and Recruitment

After enrollment, 5 patients were excluded from the trial: 3 declined to undergo the possible operation, 1 patient's AUDIT points were 13 (instead of 8 or less), and the last patient was excluded as further examination revealed bile duct stones in MRCP. Thus, in the final randomization, altogether there were 85 patients: 39 in the LCC group and 46 in the control group (Supplemental Fig. 1, http://links.lww.com/SLA/A886). No patients were lost in the follow-up.

Randomization was successful, as there were no differences in any patient parameter between the LCC group and controls (Table 1). There were 2 patients with serum GT levels over the upper normal range. Both had only 1 AUDIT score and MRCP proved to be negative. There were no statistically significant differences in imaging findings between the study groups. Only 1 patient in the LCC group had severe AP and all others had mild edematous disease. The CT scan showed that 3 patients in the control group had necrotizing pancreatitis, but MRCP was normal in all 3 patients.

Primary and Secondary Outcomes

The median follow-up of patients was 36 (5–58) months. Seventy-two patients were followed up for at least 2 years. During the follow-up, the number of patients with the recurrence after the first attack of IAP was significantly higher in the control group [14/46 vs. 4/39, $P = 0.016$, odds ratio (OR) and 95% confidence interval (CI) 5 (1.4–18)] than in the LCC group. The number of recurrences was also higher ($P = 0.003$) in the control group (Table 2). In the subgroup of patients with at least 24 months follow-up, the recurrence was still higher in the control group than in the LCC group

TABLE 1. Patient Characteristics in the Study Groups: Laparoscopic Cholecystectomy (LCC) and Control Group

	LCC, n = 39	Control Group, n = 46	*P*
Female/male	12/27	21/25	0.068*
Age (median, range), years	56 (19–84)	57 (17–79)	0.998†
Hospital stay (median, range) days	4 (1–14)	4 (2–13)	0.782†
Severe pancreatitis	1	3	0.6216*
Audit points (median, range)	2 (0–7)	2 (0–8)	0.903†
ALT (median, range) IU/L	31 (8–317)	22 (8–460)	0.703†
AST (median, range, IU/L	26 (17–107)	23 (15–100)	0.795†
ALP (median, range) IU/L	75 (43–277)	65 (31–336)	0.544†
BIL (median, range) μmol/L	9 (2–84)	9 (4–44)	0.262†
GT (median, range) IU/L	31 (7–308)	37 (7–755)	0.248†
Any abnormal liver function test	5 (13%)	5 (11%)	0.252*
CDT (median, range), %	1.5 (0.9–2.8)	1.6 (1–2.4)	0.415†
TRIGLY (median, range) mmol/L	1.2 (0.4–2.9)	1.2 (0.4–3.5)	0.540†
CT	27 (69%)	29 (63%)	0.153*
MRCP	15 (38%)	12 (26%)	0.082*

*Fisher exact test.
†Mann-Whitney *U* test.
ALP indicates alkaline phosphatase; ALT, alkaline aminotransferase; AST, aspartate aminotransferase; BIL, bilirubin; CDT, desialotransferrine; CT, computerized tomography; GT, glutamyltransferase; MRCP, magnetic resonance cholagiopancreatography; TRIGLY, triglyceride.

TABLE 2. The Recurrence of First Idiopathic Acute Pancreatitis (IAP) in the Laparoscopic Cholecystectomy (LCC) and Control Groups

	LCC, n = 39	Control, n = 46	*P*	OR†	95% CI†
Recurrence of IAP	4	14	**0.016***	5	1.4–18
Number of recurrences	8	23	**0.003***		

*Fisher exact test.
†Logistic regression (odds ratio and 95% confidence interval).

[14/37 vs. 4/35, $P = 0.008$, OR and 95% CI 4.7 (1.4–16)]. In multivariate analyses, including laparoscopic cholecystectomy, severity of disease, hospital stay, and lipid-lowering drugs, the only significant factor that influenced recurrence was LCC [$P = 0.025$, OR and 95% CI 4.6 (1.2–18)].

Recurrence had no correlation with the liver function tests. In the post hoc analysis in patients with the normal liver function, results recurrence was still significantly higher in the control group than in LCC group [13/46 vs. 4/39, $P = 0.026$, OR and 95% CI 3.6 (1.1–12)]. In the subgroup of patients with at least a 24 month follow-up, the number needed to be treated (NNT) to prevent recurrent IAP was 5 LCC in patients with IAP.

Although preoperative transabdominal ultrasound was negative in all patients, in all, 23 out of 39 patients (59%) in the LCC group had small stones in their gall bladders during surgery. The results of the liver function tests did not differ in patients with or without gallbladder stones found in LCC. We did not perform preoperative endoscopic ultrasound in this trial. Histological evaluation did not reveal chronic cholecystitis in any patients in the LCC group.

A total of 4 out of 85 (5%) patients (3 in the control and 1 in the LCC group) developed severe disease according to the revised Atlanta criteria. All 4 patients were treated in the intensive care unit (ICU) because of organ failure. A total of 2 patients in the control group underwent invasive procedures. Mini-invasive necrosectomy and endoscopic treatment with tissue glue for bleeding was performed in the first patient. The other developed bile duct stones (4.5 years after randomization) and underwent ERCP and later LCC.

In the LCC group, no further procedures were reported during the follow-up. All cholecystectomies were performed without complications and none of the patients had recurrence between randomization and LCC.

Ancillary Analysis

Altogether, 20 out of 85 (24%) patients were taking lipid-lowering drugs. Interestingly, those using these drugs had gallbladder stones in surgery less frequently than those without statins (4/23 vs. 16/23, $P = 0.0002$). In the control group, statin treatment did not effect the number of recurrences of IAP.

DISCUSSION

The main result of our randomized trial was that LCC can effectively prevent the recurrence of first IAP attack. Laparoscopic cholecystectomy is a safe method with minimal (0.12%–0.13%) mortality,[25,26] and it would thus be a justifiable treatment for IAP, when all known etiologies have been eliminated. In the control group of watchful waiting, the usual number of recurrences was 1 or 2 and those patients did not undergo cholecystectomy. According to our RCT protocol, it was ethical to follow-up patients in the control group without LCC unless severe cholecystitis or positive abdominal ultrasound was emerging. Only 1 patient later had LCC in the control group.

In a new interesting population-based study of Trna et al,[27] doubts were raised concerning the efficacy of cholecystectomy in preventing recurrent IAP. The study was based on medical records between 1990 and 2005 and included 239 patients, but unfortunately they did not report their methods for the diagnosis of IAP. The problem with such register studies is that information may be lacking for the other possible etiologies of AP. Possible alcohol abuse as an etiological factor behind recurrent pancreatitis may also be difficult to confirm from register-based studies,[28] and therefore the AUDIT questionnaire supplemented with serum CDT, and GT measurements were performed in our trial.

In a nationwide epidemiological study from the US, as many as 81,8025 cases of IAP were diagnosed between 1998 and 2007, with a mean hospital stay of 5.6 days.[29] The total cost of 1 IAP treatment period was $19,759 and mortality was higher in IAP patients than in patients with biliary or alcoholic pancreatitis. The diagnostic work-up and treatment of IAP is therefore challenging and expensive. In the present prospective trial, we tried very carefully to exclude all possible etiological factors for AP. Transabdominal ultrasound was performed at least 2 times, and multiple laboratory tests and all conventional imaging modalities were performed as well. In spite of this, almost 60% of removed gall bladders included small stones or sludge. This indicates that transabdominal US is not as reliable as we might think in AP, and that in these cases the pancreatitis episodes were most likely not idiopathic but biliary in nature.

A major drawback of our diagnostic work-up was that we did not perform endoscopic ultrasound (EUS) to detect more reliable small gall stones or biliary sludge. Mariani et al[30] compared MRCP, EUS, and ERCP with secretin stimulation to detect biliary and/or pancreatic abnormalities in patients with IAP. They found that, together, these 3 examinations established the possible etiology for AP in 64% of cases. Secretin-stimulated EUS found ductal and parenchymal abnormalities with the highest frequency (80%) and both EUS and MRCP were superior to ERCP in detecting pancreatic ductal abnormalities.[30] Such patients are primarily diagnosed as having IAP.[18] Half of our centers were central hospitals in Finland with no possibility to perform EUS. This is the case for most nonacademic hospitals worldwide. Our diagnostic work-up to diagnose IAP included common laboratory tests, an AUDIT questionnaire, and conventional imaging, including MRCP, which all are available in nonacademic hospitals. In cases with elevated liver function results, but no gallstones in US, MRCP was also used to exclude other etiological factors. The diagnosis of IAP in the present trial, followed the new guidelines, except that EUS was not done. [31] However, our protocol might be closer to the clinical practice in many hospitals. The noncompliance of all guidelines outside the trials has been well recognized.[32,33]

It has been suggested that alanine aminotransferase above 150 U/l could predict a biliary etiology.[33,34] In the present trial, only 1 patient in the LCC group had such a high level, but no gall stones. Other factors, such as fatty liver, may also increase liver enzymes. Other etiologies such as hyperlipidemia or hypercalcemia were also systematically excluded by laboratory tests.

In patients with pancreatic sphincter disorder, pancreatic duct stenting has also been used.[35] In a prospective randomized study by Jacob et al,[35] comparing no stent versus stent insertion into the pancreatic duct, the recurrence in IAP patients was more common in the no-stent than in the stent group [8/15 (53%) vs. 2/19 (11%), $P < 0.02$]. In light of the present findings, this may be explained by the stent prevention of temporary duct obstruction by the passing microlithiasis. It has been suggested that bile crystal analysis, a marker for microlithiasis, should be considered in patients with IAP and negative MRCP, EUS, and ERCP.[7] Empiric cholecystectomy has also been recommended.[36–38] However, the role of cholecystectomy in preventing recurrent IAP has been debated for at least 30 years without irrefutable conclusion due to the lack of randomized trial this far.

One interesting finding was that patients taking lipid-lowering medication had stones or microlithiasis less frequently during LCC, which is in contrast to the claims that these lipid-lowering drugs may induce pancreatitis.[39–44] Instead, our trial concurs with a recently published meta-analysis where the risk ratio of pancreatitis was lower (0.77) in patients taking lipid-lowering medication.[43] It is logical that lipid-lowering drugs could lower the risk of pancreatitis by decreasing cholesterol saturation in the bile.[44] The connection between lipid-lowering drugs and pancreatitis has been studied in biliary pancreatitis and in IAP.[43,44] Our recent study indicated that statin therapy was significantly more frequent in patients with IAP than in other known etiologies of AP.[45] The positive or negative association does not necessarily mean causality, ie, that statin therapy causes or reduces the incidence of IAP. The role of statins in the etiology and treatment of IAP warrants further studies.

In conclusion, our trial supports the statement that many idiopathic pancreatitis have in fact gall stone etiology despite undetectable with liver chemistry, transabdominal ultrasound or selective MRCP. Others have proposed microcrystal analysis and EUS to improve the detection of gall stone etiology, but these examinations lack largely worldwide in nonacademic hospitals. Our trial demonstrates that empiric LCC can effectively prevent recurrence in IAP with NNT value of 5. Although our sample size was small, we do not believe that there was no type 2 error in the power calculation. More studies with randomized patients are needed to confirm the results of our trial.

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DISCUSSANTS

K.C. Conlon (Dublin, Ireland):

The incidence of acute pancreatitis (AP) appears to be increasing in the Western world in part due to increasing alcohol consumption. However, despite extensive contemporary investigations, up to 30% of cases continue to be classified as idiopathic. In this interesting Finnish prospective, multicenter, randomized clinical trial, the authors have attempted to answer the question as to whether a prophylactic laparoscopic cholecystectomy could prevent recurrent attacks of idiopathic acute pancreatitis (IAP).

You randomized 85 patients with presumed IAP, 39 of whom underwent a cholecystectomy and 46 who were observed. At a median follow-up of 36 months, there was a significant reduction in the episodes of recurrent pancreatitis in the surgical group, leading the authors to conclude that LCC can effectively prevent the recurrence of IAP when all other possible etiologies of pancreatitis are carefully excluded. However, before we accept the results, a number of issues require clarification.

Transabdominal ultrasonography (US) was performed in all cases. When was it performed during the initial episode? Was it performed by a consultant, trainee or technician? Do the authors have any sense of the negative predictive value of US in this patient cohort, particularly since 59% of patients undergoing a cholecystectomy were noted to have small stones at surgery? MRCP was only performed in less than 30% of cases. This would appear to be low, as many would advocate its use routinely to exclude ductal calculi and anatomical abnormalities particularly following a negative US. How was it decided which patient would undergo an MRCP? Was secretin used? If MRCP was not performed, how did you exclude pancreas divisum?

While EUS may not be available in every institution, it is part of a contemporary diagnostic algorithm particularly for recurrent IAP. Could their data suggest that a significant cohort would have benefited from this test? Would they propose a selective referral pathway? Was autoimmune pancreatitis excluded? No data is given regarding smoking history. As smoking has been shown to be a major prognostic variable for developing recurrent pancreatitis, was this examined? If not, could it be a confounding variable?

What investigations were performed following the second episode of AP? How many of these patients remained idiopathic? How many were found to have biliary pancreatitis?

While the authors correctly state that cystic fibrosis (CF) is uncommon in Finland, the CFTR mutations of interest in RAP are not associated with the typical presentation of CF and therefore CFTR mutations may be more prevalent than heretofore assumed and should be assessed with PRSS1 and SPINK-1 particularly in young patients with IAP. Patients with a family history of AP were only tested in this trial. How did the authors exclude sporadic cases, particularly in young patients with IAP?

Finally, how do the authors explain the apparent risk reduction of laparoscopic cholecystectomy in the 41% of patients who did not have stones or sludge? This is an important provocative trial and the authors should be congratulated. I enjoyed reviewing their well-written manuscript. I wish to thank the Scientific Program Committee for giving me the opportunity to examine this work.

Response From H. Paajanen (Kuopio, Finland):

In acute pancreatitis (AP), the first transabdominal ultrasound (or CT) was performed when the patient came into the hospital, usually after 2 or 3 days of admission. Transabdominal ultrasound was not a very good examination at this time because bowel gas disturbs reliable imaging of biliary etiology. The ultrasound was always performed by a senior consultant radiologist. The second ultrasound was performed in the outpatient clinic 1 or 2 months after the first attack. In our hands, transabdominal ultrasound was not very good to image small gallbladder stones in patients with AP.

MR cholangiography was not available in every nonuniversity hospital during the beginning of the study. We did not use sercetin-stimulated MRI. We think that MR cholangiography may not depict very small crystals or small stones in common bile duct. A more liberal use of secretin-stimulated MR cholangiography and endoscopic ultrasound is, however, recommended and a topic of our further studies. Cystic fibrosis is very rare in the adult population in Finland. It is basically a pediatric disease and we have never heard about it causing AP in our country. Therefore genetic testing was not performed in every patient. We did not analyze smoking and that is a weakness of our study.

O. Farges (Paris, France):

I have 2 questions.

First, if I understand it correctly, 60% of the patients in the cholecystectomy group turned out to have a biliary lithiasis. Did you perform a cholecystectomy in patients of the control group who experienced recurrent pancreatitis and did these patients also have a high prevalence of lithiasis?

Second, most of the patients had mild pancreatitis. There are 2 frequently overlooked etiologies of recurrent mild pancreatitis despite a cholecystectomy: One is IPMN and the other is the Low Phospholipid Associated Cholestasis (LPAC) syndrome. Have you looked for these etiologies in patients with recurrent pancreatitis?

Response From H. Paajanen (Kuopio, Finland):

We did not perform cholecystectomy in the controls. IPMN needs imaging studies (CT or MRI) and in our trial we did not identify IPMN or LPAC patients.