In up to 20% of acute pancreatitis the etiology is unknown and term idiopathic pancreatitis is used. We found that patients with idiopathic acute pancreatitis use statins more often than patients with alcohol or biliary pancreatitis and patients who use statins may have an increased risk of pancreatitis. We also found that many idiopathic pancreatitis patients have small gallstones, even though none were detected and recurrent acute idiopathic pancreatitis is less common after cholecystectomy.
Role of Statins in Acute Pancreatitis and Symptomatic Cholelithiasis
Role of Statins in Acute Pancreatitis and Symptomatic Cholelithiasis

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ABSTRACT

Cholesterol is essential for the functioning of all human organs. Bile acids are synthesized from cholesterol in liver and are stored in the gallbladder. Gallstone disease is a common abdominal condition in developed countries. Some 80-90% of gallstones formed within the gallbladder consist mainly of cholesterol in the western world. The prevalence of cholelithiasis is increasing.

Acute pancreatitis (AP) is inflammation of the pancreas and ranges from mild symptoms to a life-threatening or life-ending process. It may progress to a chronic form leading to maldigestion and diabetes mellitus. The main causes for AP are alcohol use or small gallstone migration with obstruction of bile and pancreatic enzymes. Cholelithiasis is thus associated with pancreatitis. In up to 20% of AP the etiology is unknown. There are many possible etiologies for idiopathic pancreatitis, including drug-induced pancreatitis or microlithiasis. In animal models statins have been shown to decrease the size of gallstones.

Hypercholesterolemia is a major cause of coronary heart disease and other manifestations of vascular atherosclerosis. Statins are used for the treatment of hypercholesterolemia in order to prevent cardiovascular events. In Finland there has been a 11-fold increase in statin use between 1995 and 2000 and approximately 660,000 individuals (12% of the population) purchased statins in 2012. Coinciding with the increase in statin use, there has been a notable increase in the number of patients with AP. The evidence concerning the association between statins and the risk of acute pancreatitis is inconclusive. Findings in case reports and two case–control studies have suggested that statins increase the risk of acute pancreatitis, whereas a recent meta-analysis suggested a protective association.

To investigate the relationship of statins and pancreatitis, we carried out two studies in Kuopio University Hospital (461 admissions of patients with AP and 1140 patients with gallstones between 2008 - 2010) including patient cohort during (272 statin users and 272 controls). We found that statin therapy was significantly more frequent in patients with idiopathic acute pancreatitis than in other known etiologies. In patients with cholecystectomy there was no significant difference in outcome between the statin users
and non-users, although statin users had more polypharmacy (including drugs that cause bleeding) and cardiovascular illnesses than non-users. The mean operation time for laparoscopic cholecystectomy was 10% shorter for the patients with statin use than for the patients without.

Together with the Finnish Medicine Agency (Fimea) we carried out a large nationwide study and found that statin use was associated with an increased incidence of AP (OR 1.25, 95% CI 1.13-1.39). The incidence was elevated especially during the first year of use both among current and former statin users.

Finally in a randomized study of 85 idiopathic pancreatitis patients (39 in the laparoscopic cholecystectomy and 46 in the control group) we found that 59% of operated patients had small gallstones in their gallbladder, although preoperative transabdominal ultrasonography was negative. We also found that recurrence of IAP was less common in patients undergoing LCC. Interestingly, the patients using lipid-lowering drugs had gallbladder stones in surgery less frequently than those without statins.

Based on these data it is concluded that statin medication seems to affect the bile metabolisms also humans and patients who use statins have increased risk of pancreatitis. Cholecystectomy in statin-using patients is as safe as in non-users although statin users had more comorbidities than non-users. Recurrence of idiopathic pancreatitis can be prevented by laparoscopic cholecystectomy.
Kolesteroli on ihmiselinten toiminnalle välttämätöntä. Sappihappoja syntetisoidaan maksassa kolesterolista ja varastoidaan sappirakossa. Sappikivitauti on yleinen kehittyneissä maissa ja sen esiintyvyys on kasvussa. Länsimaissa sappirakossa muodostuneista sappikivistä noin 80-90% koostuu pääasiassa kolesterolista.

Statiinien käyttäjillä esiintyi useammin etiologialtaan epäselvä haimatulehdus kuin sappikivitautin tai alkoholin aiheuttama haimatulehdus. Statiineja käyttävien potilaiden sappileikkausten tulokset olivat yhtä hyvät kuin ei-käyttävien, vaikka statiineja käyttävät potilaat olivat sairaampia ja he söivät useita mm. vuotoa aiheuttavia lääkkeitä. Kuitenkin statiineja käyttävien potilaiden sappileikkaus sujui 10% nopeammin kuin niiden joilla ei ollut statiineja käytössä.

Yhteistyössä Fimean (Suomen lääkealan ja turvallisuuskeskus) kanssa teimme laajemman kansallisen tutkimuksen statiineista ja pankreatiitista. Kansallisessa tutkimuksessa löysimme statiinen käytön lisäävän äkillisen haimatulehduksen riskiä merkittävästi (OR 1.25, 95% CI 1.13-1.39). Riski oli kohonnut erityisesti statiinien käytön ensimmäisen vuoden aikana sekä uusilla että vanhoilla käyttäjillä.

Lisäksi havaitsimme, että 85 epäselvää haimatulehdusta sairastavalla potilaalla (39 tähystysellinen sappirakon poisto ja 46 kontrollia) jopa 59%:lla oli pienet sappirakkokivet, vaikka ennen leikkausta tehdyssä ultra-äänitutkimuksessa niitä ei havaittu. Haimatulehduksen uusiutuminen oli myös tavallisempi niillä potilailla, joilla ei sappirakkoa poistettu. Yllättäen statiinien käyttäjillä oli vähemmän sappikiviä kuin ei statiinien käyttäjillä.

Statiinilääkitys näyttää vaikuttavan myös ihmisellä sapen aineenvaihduntaan ja lisäävän haimatulehduksen riskiä. Sappirakon poistoleikkaus on statiinilääkitystä käytettävälle potilaalle yhtä turvallinen ja jopa nopeampi kuin niille, joilla ei ole statiinia käytössä. Epäselvän haimatulehduksen uusiutuminen voidaan estää monissa tapauksissa tähystysellisellä sappirakon poistolla.

Yleinen Suomalainen asiasanasto: haimatulehdus; kolesteroli; lääkehoito; sappikivet; sappitaudit; statiinit
to Sari, Ville and Joonas
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Kuopio, September 2015

Jukka Pulkkinen
List of the original publications

This dissertation is based on the following original publications:


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4 PATIENTS AND METHODS

4.1 Patients

4.2 Methods

4.1 Statistics

5 RESULTS

6 DISCUSSION

7 CONCLUSIONS

8 FUTURE PERSPECTIVES

9 REFERENCES

APPENDIX
Original Publications I-IV
Abbreviations

ADR       adverse drug reaction
AP        acute pancreatitis
BMI       body mass index
CP        chronic pancreatitis
ERCP      endoscopic retrograde cholangiopancreatography
Fimea     Finnish Medicines Agency
HDL       high-density lipoprotein
HMG CoA   3-hydroxy-3-methylglutaryl coenzyme A
LC/LCC    laparoscopic cholecystectomy
LDL       low-density lipoprotein
IAP       idiopathic acute pancreatitis
IP        idiopathic pancreatitis
MRCP      magnetic resonance cholangiopancreatography
1 Introduction

The French physician-chemist François Poulletier was the first to isolate pure cholesterol from gallstones in 1784 (Endo 2010). Today we know that the majority of gallstones formed within the gallbladder consist mainly of cholesterol (70%-90%) in the Western world (Marschall, Einarsson 2007). Some of the first studies of AP were by Reginald Heber Fitz, a pathologist, who described the clinical features of acute pancreatitis in 1889 and subtyped it into hemorrhagic, suppurate, or gangrenous pancreatitis (Reginald 1889). However, he believed that pancreatitis was the result of gastroduodenitis. Certainly, the ensuing decades witnessed a number of advances in the diagnosis, prognosis, and therapy of acute and chronic pancreatitis (Rustgi 2013). Based on Opie’s "obstruction theory" of 1901 and experimental data, it is now widely accepted that the gallstone passage into or through the terminal biliopancreatic ductal system triggers AP by causing pancreatic ductal obstruction (Runzi, Layer 1997).

Cholesterol is essential for the functioning of all human organs. Bile is a mixture of bile acids, cholesterol, phosphatidylcholine, and bilirubin. Bile acids are synthesized from cholesterol in hepatocytes. Synthesized bile acids are stored in the gallbladder and secreted into the duodenum in response to feeding, contributing to digestion of lipids and lipid-soluble vitamins and they play critical roles in regulation of metabolism (Ma, Patti 2014). In the mid-1960s nutritional physiologist Ancel Keys showed the epidemiologic connection between blood cholesterol and coronary atherosclerosis. Hypercholesterolemia reflecting LDL-accumulation in intimal layers of vasculature is a major cause of coronary heart disease and other vascular atherosclerotic diseases. Cardiovascular diseases are among the most common causes of death in the Western world. Vascular atherosclerosis causes also vascular dementia and precedes thrombotic events that cause tissue damage by blocking of major blood vessels. Japanese biochemist Akira Endo isolated statins from fungi in 1972 (Penicillium citrinum) (Endo 2010). Statins are potent inhibitors of cholesterol synthesis in the liver and they are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase. This reductase coenzyme A regulates the rate-limiting step in cholesterol biosynthesis. After many intermediate steps and stages of development, lovastatin become the first commercial statin in September 1987 (Stossel 2008, Endo 2010).

Today a 30% reduction in heart attacks has been documented after treatment with statins. Furthermore, millions of individuals worldwide use statins for primary prevention and avoid heart attacks (Stossel 2008, Taylor et al. 2013). Coinciding with the increase in statin use, there has been a notable increase in the number of patients with AP. The findings in case reports and two case-control studies (data pooled together in a meta-analysis) have suggested that statins increase the risk of AP (Singh, Loke 2006, Etienne, Reda 2014), whereas a recent meta-analysis suggested a protective association (Preiss et al. 2012). The
biological mechanisms behind statin induced AP remain unclear, and the evidence concerning the association between statins and the risk of acute pancreatitis is inconclusive.

In 1988 it was reported that the molar percent of cholesterol in human gallbladder bile was reduced during lovastatin therapy and thus the lithogenic index of gallbladder bile was also decreased. This finding suggests that the risk of cholesterol gallstone formation is reduced during lovastatin therapy. The possibility that the drug might actually promote cholesterol gallstone dissolution started a new research direction (Freeman et al. 1988, Wang et al. 2013). Currently we do not yet have a full understanding of the role of statins in AP or in gallstone disease. There are very few studies on the effect of statins treatment on gallstone disease or AP. The hypothesis of our studies was that statins have significant role in the metabolism of gallstones in humans. Some idiopathic AP may also be induced by statins. We made two cohort studies, nation wide epidemiologic study and randomized treatment study to find more evidence of statins role in symptomatic gallstones and AP in humans.
2 Review of the literature

Pancreatitis is inflammation of the pancreas that progresses from acute (sudden onset; duration < 6 months) to recurrent acute (> 1 episode of AP) to chronic (duration > 6 months) (LaRusch, Solomon & Whitcomb 1993). The clinical manifestations of pancreatitis range from mild symptoms to a life-threatening or life-ending process (Martin, Hein 2013).

2.1 Pancreatitis in Finland and elsewhere

Acute pancreatitis is one of the most common gastrointestinal disorders requiring acute hospitalization worldwide, with a reported annual incidence of 13-45 cases per 100,000 persons (Working Group IAP/APA Acute Pancreatitis Guidelines 2013).

Gallstones are the most common cause of AP worldwide. Alcohol is the second most common cause worldwide, but an episode of alcohol pancreatitis requiring admission to hospital may represent an exacerbation of chronic pancreatitis rather than true recurrent AP (Kingsnorth, O'Reilly 2006, Vonlaufen et al. 2014).

Alcohol is the leading cause of AP in Finland, and the number of patients with AP has been increasing in Finland. The annual incidence of AP in Finland was 70 per 100,000 in the 1980s. The incidence of hospitalizations for acute alcohol-induced pancreatitis has increased among the middle-aged in both genders, from 60 to 102/100,000/year in men, and from 5 to 21/100,000/year in women between 1997 and 2007. The female-to-male ratio in hospitalization increased 50% during this time (Jaakkola, Nordback 1993, Sand, Valikoski & Nordback 2009).

There are also regional differences in demographic distributions; alcohol-related pancreatitis is more common in the Western world and Japan than in other Asian countries, and there is wide variation in the prevalence of a form of chronic pancreatitis (CP) that is endemic to tropical countries (20–125/100,000 persons reported in 2 parts of South India) (Yadav, Lowenfels 2013).

Significant differences in the incidence and etiology of AP exist between and within countries, reflecting differences in the prevalence of risk factors and causes might vary between countries and over time in single country. The incidence of first-attack AP increases with age. Particularly gallstone related AP is more common in female subjects and the elderly. Alcoholic AP is more common in middle-aged male subjects, whereas idiopathic AP affects both sexes equally (Yadav, Lowenfels 2006).
2.2 Acute pancreatitis

Acute pancreatitis is a reversible inflammatory process of the pancreas. Although the disease process may be limited to pancreatic tissue, it also can involve peripancreatic tissues or more distant organ sites. AP may occur as an isolated attack or may be recurrent (Carroll et al. 2007). The range of symptoms and disease course vary from person to person (LaRusch, Solomon & Whitcomb 1993).

Acute pancreatitis can be subdivided into two types: interstitial edematous pancreatitis and necrotizing pancreatitis. The early phase, which usually lasts for the first week, is followed by a second later phase, which can run a protracted course from weeks to months (Banks et al. 2013).

According to the 2012-revised Atlanta classification system, AP can be classified as mild, moderate, or severe. The overall mortality of AP is approximately 5% (Phillip, Steiner & Algul 2014). This revised classification differentiates acute peripancreatic fluid, pancreatic pseudocyst, acute necrotic collections and walled-off necrosis (Banks et al. 2013). Patients with mild AP (no organ failure or systemic or local complications) are frequently discharged within 3–7 days of onset of illness. Mild AP has a very low mortality rate (< 1 percent) (Carroll et al. 2007, Banks et al. 2013). Patients with moderately severe AP have one or more of transient organ failure, defined as organ failure lasting less than 48 h. The mortality of moderately severe AP is far less than that of severe AP. Severe AP is persistent single-organ or multiorgan failure that is present more than 48 h. Most these patients who have pancreatic necrosis have mortality of at least 30% (Lankisch, Apte & Banks 2015). Patients who develop more than 48 hours lasting organ failure within first few days of the disease are at increased risk of death, with a mortality reported to be as great as 36–50%. If this necrosis develops an infection, there is an even higher mortality (Banks et al. 2013).

Patients with severe acute pancreatitis and organ failure are at high risk of suffering from intra-abdominal hypertension with incidence varying from 60% to 85%. Intra-abdominal hypertension may further accelerate the development of abdominal compartment syndrome, which is the end product of intra-abdominal hypertension and characterized by severe organ dysfunction, with respiratory, cardiovascular and renal dysfunction. Persistent organ failure was found to be a major determinant of mortality (De Waele 2014).

2.3 Chronic pancreatitis

Chronic pancreatitis is an inflammatory disease of the pancreas characterized by progressive fibrotic destruction of the pancreatic secretory parenchyma. Despite the heterogeneity in pathogenesis and involved risk factors, processes such as necrosis/apoptosis, inflammation or duct obstruction are involved (Brock et al. 2013).
Chronic pancreatitis typically manifests as episodic or continuous mild to severe abdominal pain. CP progresses to maldigestion and pancreatic exocrine and endocrine insufficiency (diabetes secondary to pancreatic diseases is commonly referred to as pancreatogenic diabetes or type 3c diabetes mellitus) (LaRusch, Solomon & Whitcomb 1993, Ewald, Hardt 2013). CP, although lower in incidence than AP, significantly reduces patients’ quality of life.

Acute pancreatitis may progress to recurrent AP and then to CP in a disease continuum. Overall, approximately 20% to 30% of patients with AP have a recurrence, and approximately 10% develop CP. Progression from AP to CP occurs more frequently with continued exposure to alcohol or smoking and in patients with genetic causes of pancreatitis (hereditary pancreatitis) (Yadav, Lowenfels 2013).

2.4 The etiology of pancreatitis

Worldwide alcohol is the second most common cause of AP after gallstones. Other causes are more uncommon or controversial (Wang et al. 2009).

2.4.1 Alcohol pancreatitis

Alcohol abuse is commonly associated with the development of both acute and chronic pancreatitis. Excessive alcohol intake is associated with possible direct pancreatic damage. Pancreatic injury due to alcohol consumption ranges from isolated episodes of AP to chronic manifestations. Alcohol is the most common cause for CP (Yadav, Lowenfels 2013). Only a small percentage of human beings who abuse alcohol develop pancreatitis, which indicates that alcohol abuse alone is not sufficient to initiate clinical pancreatitis. It is widely believed that ethanol sensitizes the pancreas to injury and additional factors trigger the development of overt pancreatitis. Ethanol and its metabolites have a number of deleterious effects on acinar cells and alcohol also affects pancreatic stellate cells, but the exact mechanism how ethanol sensitizes the pancreas to pancreatitis is not entirely known (Clemens et al. 2014).

In United States an alcohol etiology accounts around 50%-55% of chronic pancreatitis. In European series there is some variability between countries. For example, in Italy the percentage was 43%-79%, Germany 78%, Denmark 44%, Czech Republic 60% and Switzerland 71% (Herreros-Villanueva et al. 2013).

A series of CP published in Mexico showed that 68% of patients had an alcoholic etiology, while alcohol was the responsible factor in 90% of patients in Brazil, 80% in South Africa and 33% in India (Herreros-Villanueva et al. 2013).
Smoking is an independent risk factor for AP and CP, and its effects could synergize with those of alcohol (Yadav, Lowenfels 2013). Smoking increases the risk of a first event of acute non-gallstone-related pancreatitis by approximately two-fold (Sadr-Azodi et al. 2012).

2.4.2 Gallstone pancreatitis

Most episodes of biliary pancreatitis are associated with transient impaction of the bile stone in the ampulla of Vater (that causes obstruction of the pancreatic duct, with ductal hypertension) or passage of the stone through and into the duodenum. Microlithiasis or biliary sludge can cause AP too (Sakorafas, Tsiotou 2000, Lankisch, Apte & Banks 2015).

Obesity

Obesity and rapid weight loss after bariatric surgery are risk factors for the formation of cholesterol gallstones and exposes patients to an increased risk of gallstone-related pancreatitis and other complications. The incidence of AP has been steadily increasing, in parallel with the increasing prevalence of obesity, in the last decades.

Whereas obesity is a true risk factor for cholesterol cholelithiasis and biliary sludge, obesity can also act as an independent risk factor for a more severe course of AP. Obesity might also act on AP via increased abdominal fat and an overactive systemic inflammatory response (Bonfrate et al. 2014).

Pregnancy

Acute pancreatitis in pregnancy is a rare but severe disease with a possibility of maternal-fetal mortality. AP is estimated to occur in 1 per 1000 to 1 per 12 000 pregnancies and AP usually occurs during the third trimester. Pregnancy does not primarily predispose pregnant women to pancreatitis, but it does increase the risk of cholelithiasis and biliary sludge formation (Stimac, Stimac 2011, Ducarme et al. 2014).

2.4.3 Metabolic pancreatitis

Acute pancreatitis secondary to hypertriglyceridemia must not be misdiagnosed. Severe hypertriglyceridemia (levels of triglycerides > 11,3 mmol/l) is a well-documented cause of AP (Kemppainen, Puolakkainen 2007, Stefanutti, Labbadia & Morozzi 2013). Hypertriglyceridemia is estimated accounting for approximately up to 10% of all cases and up to 50% of all cases in pregnancy. Both primary (genetic) and secondary disorders of lipoprotein metabolism: obesity, diabetes mellitus, pregnancy, alcohol and different drugs may be associated with hypertriglyceridemic pancreatitis. The role of alcohol in
hypertriglyceridemia is controversial. Severe hypertriglyceridemia may be attributed to alcohol. Another hypothesis is that alcohol alone does not cause hypertriglyceridemia, but more likely leads to an exacerbation of an underlying genetically based hypertriglyceridemia (Ewald, Hardt & Kloer 2009). Most instances of hypertriglyceridemia are asymptomatic. However, it can present as disturbances in multiple organ systems, including the cardiovascular, renal, neuropsychiatric, and gastrointestinal system.

The most common cause of an elevated serum calcium level is primary hyperparathyroidism, which has an annual incidence of about 30 cases per 100,000 in the Europe and United States. Hypercalcemic pancreatitis is rare and is an uncommon first manifestation of primary hyperparathyroidism. The hypercalcemia seen with primary hyperparathyroidism has been associated with both acute and chronic pancreatitis since the mid-20th century. It is important to recognize pancreatitis in patients with primary hyperparathyroidism and, conversely, to consider primary hyperparathyroidism by checking serum calcium levels in patients, who present with an unexplained pancreatitis (Bai et al. 2012). Multiple endocrine neoplastic type 1 (MEN1) and type 2A (MEN2A) are rare, an autosomal dominant inherited conditions that predisposes primary hyperparathyroidism (Moline, Eng 2011).

Another, quite rare reason of an elevated calcium level is pancreatic neuroendocrine tumor (Bai et al. 2012). Other causes of hypercalcemia and acute pancreatitis include bony metastases or multiple myeloma, vitamin D toxicity, sarcoidosis, and total parenteral nutrition and infusions of perioperative high-dose calcium during cardiopulmonary bypass (Kota et al. 2013). Milk-alkali syndrome is an uncommon etiology for pancreatitis. It is caused by increased calcium and alkali ingestion, causing hypercalcemia accompanied by metabolic alkalosis and renal failure (Daniel, Wadman & Branecki 2014). Lowered parathyroid hormone levels characterize these conditions, in contrast to primary hyperparathyroidism.

Other metabolic causes of pancreatitis are porphyria and rarely the copper metabolism disorder Wilson’s disease (Bandmann, Weiss & Kaler 2015).

Type 2 diabetes mellitus

According to a meta-analysis, patients with type 2 diabetes mellitus may have an 80% increased risk of AP. Diabetes is associated with a higher risk of cholelithiasis and the incidence of gallstone-related pancreatitis seems to be higher in patients with type 2 diabetes mellitus than that in a nondiabetic population. Type 2 diabetes mellitus is related to obesity and hyperlipidemia, both of which are risk factors for pancreatitis. It has also been found that type 2 diabetes mellitus is associated independently with an increased risk of AP (Yang et al. 2013). On the other hand anti-diabetic drugs, including incretins, might increase the risk of AP (Kikuta, Masamune & Shimoregawa 2015).
2.4.4 Pancreatitis after ERCP

Acute pancreatitis remains the most common complication of endoscopic retrograde cholangiopancreatography (ERCP). Post-ERCP pancreatitis is reported to occur in 2–10% of unselected patient samples and up to 40% of high-risk patients. Risk factors for post ERCP-pancreatitis are young age, female gender, suspected sphincter of Oddi dysfunction, a history of post ERCP-pancreatitis, normal serum bilirubin, the number of cannulation attempts and contrast injections or trauma to the pancreatic duct (Thaker, Mosko & Berzin 2014, Ding, Zhang & Wang 2014). Post ERCP-pancreatitis is mild or moderate in about 90% of cases (Lankisch, Apte & Banks 2015).

2.4.5 Genetic pancreatitis

Growing evidence from genetic studies on pancreatitis suggested that it might be an inherited disease. Hereditary pancreatitis is a rare cause of CP. The prevalence was evaluated to 0.3/100000 in Western Countries. Genetic disorders are due to mutations of the PRSS1 gene on the long arm of the chromosome 7, encoding for the cationic trypsinogen. First symptoms begin since childhood, mainly before 10 years old. The main symptoms are pancreatic pain and AP (>70%) (Kim et al. 2003, Rebours, Levy & Ruszniewski 2012). In addition to this, a number of other mutations or polymorphisms in genes that have a role in inhibition, regulation or modulation of the pancreatic trypsin activity, secretory function and inflammatory injury, respectively have been identified (Ravi Kanth, Nageshwar Reddy 2014).

2.4.6 Idiopathic pancreatitis

The term “idiopathic pancreatitis” (IP) was originally designated to cases of pancreatitis wherein a diagnosis could not be made by history, physical examination, laboratory studies and noninvasive imaging modalities such as abdominal ultrasonography/computerized tomography. Previously, this nomenclature had accounted for 8%-44% of cases being termed “idiopathic”. Recent new laboratory methods and technological advances revealed the etiology in 80% of patients previously labeled as having “idiopathic pancreatitis” (Lee, Enns 2007). Several diagnoses have been suggested to explain idiopathic AP (table 1).
Table 1. Possible disease to explain idiopathic pancreatitis.

<table>
<thead>
<tr>
<th>Disease</th>
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<tr>
<td>Microlithiasis</td>
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<tr>
<td>Anomalous biliary microlithiasis</td>
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<tr>
<td>Pancreatic infarct</td>
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<tr>
<td>Autoimmune disease</td>
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The term biliary microlithiasis denotes the presence of small stones ≤ 3 mm in the gallbladder or biliary tree that are not imaged on conventional ultrasonography. Smaller gallstones carry a higher risk of AP than larger ones and this supports the possible role of biliary microlithiasis in the etiology of AP. Microlithiasis is considered to cause up to one third of all cases of IP (Lee, Enns 2007). Microlithiasis or biliary sludge in the gallbladder lumen increases the risk for colicky pain or AP. The risk of developing typical biliary pain is low (2.0%-2.6% per year) and the overall risk rate for complications (yearly incidence 0.3%) and gallbladder cancer (0.02%) are very low (Portincasa et al. 2012).

The role of sphincter of Oddi dysfunction as a cause of idiopathic recurrent AP remains controversial, but available data support an association of biliary microlithiasis with altered biliary and pancreatic sphincter of Oddi function (Abeyesuriya, Deen & Navarathne 2010, Lankisch, Apte & Banks 2015).

Pancreas divisum is a suspected but controversial cause. It arises from a failure of the dorsal and ventral ducts to fuse in embryo so that most of the pancreatic juice flows through the minor pancreatic duct and papilla (Kingsnorth, O’Reilly 2006). Anomalous pancreaticobiliary ductal union has also been found to be associated with AP, but the exact association remains to be elucidated (Wang et al. 1998).

Choledochocele is a rare congenital or acquired condition in which the intramural segment of the distal pancreaticobiliary ductal system is dilated and herniates into the duodenal lumen. They vary in size from a few millimeters to several centimeters. Of the five types, only type III cysts have been associated with idiopathic acute recurrent pancreatitis. AP develops when the cyst or its contents (sludge or stones) obstruct pancreatic duct outflow (Levy, Geenen 2001).

Annular pancreas is a rare congenital anomaly. Very few cases of pancreatitis related to annular pancreases have reported. It consists of a ring of pancreatic tissue encircling the duodenum. Clinical manifestations may ensue at any age (Jarry et al. 2011).
Any mass that obstructs the main pancreatic or biliary ducts, benign or malignant can result in AP. It has been estimated that 5%-14% of patients with pancreaticobiliary tumors, present with apparent IP (Lee, Enns 2007). Also an acute inflammatory process may mask the presence of an underlying lesion in the pancreas making lesion diagnosis difficult (Mujica, Barkin & Go 2000, Meng et al. 2014). CP can mimic carcinoma too. Groove pancreatitis is a segmental CP. The most common cause of a head mass in CP is inflammatory, so called “groove pancreatitis”, and occurs as a result of defective restitution after recurrent attacks of AP. An inflammatory mass in the head of pancreas is observed in approximately 30%-75% of all surgical patients suffering from CP. The majority of pancreatic tumors (70%) are located in the head of the pancreas, and inflammatory masses in CP also seem to prefer the head region (Perumal et al. 2013, Tezuka et al. 2010).

Celiac disease is a common autoimmune enteropathy, with prevalence around 1% in the general population (Petrarca et al. 2014). A few resent studies have found that celiac disease is an important risk factor for pancreatitis, but the magnitude of the risk is unclear because of inaccuracies of the diagnoses of AP and CP (DiMagno, DiMagno 2013).

In all, 525 different drugs are listed in the World Health Organization (WHO) database suspected to cause AP as a side effect (Nitsche et al. 2012). The true incidence of drug-induced pancreatitis is unknown. Evidence associating drugs with AP is largely based on individual cases (adverse drug reaction, ADR) and therefore is classified as type B ADR (see chapter 2.7). Since no specific test for establishing the diagnosis of drug-induced pancreatitis is available, the diagnosis is usually based on excluding all other common causes (Hung, Abreu Lanfranco 2014). In older studies, the incidence of drug-induced pancreatitis has been estimated between 0,1–2%. In more recent studies an incidence of up to 5,3% has been reported. Drug-induced pancreatitis is still considered to be a rare event, but in most studies it is the third most frequent cause of pancreatitis (Nitsche et al. 2012). The mechanisms of drug-induced pancreatitis are unknown and may vary with different drug classes. Theories include immune-mediated inflammatory response, metabolic effects, arteriolar thrombosis, direct cellular toxicity and pancreatic duct obstruction (Johnson, Loomis 2006).

A wide variety of infectious agents have been associated with AP. The causative role of infectious agents such as bacteria, viruses, fungi and parasites remains a controversial issue; their true incidence is unknown because they co-exist quite often with other noninfectious causes. Mumps infection as a cause of pancreatic disease was speculated as early as 1817. Currently, it is not yet clear whether infectious agents can cause pancreatitis alone or in combination with at least one of the aforementioned conditions. Coxsackie virus, adenovirus, hepatitis B virus, CMV and increasingly HIV has been reported in the literature as rare causes of acute pancreatitis (Konstantinou et al. 2009, Parenti, Steinberg & Kang 1996).
Pancreatic infarcts may occur in patients with underlying atherosclerotic vascular disease, but they are unusual because the pancreas is richly perfused from several different arterial sources. CP is associated with histological changes in the vasculature and decreased pancreatic blood flow (Lewis, Reber & Ashley 1998). Ischemic pancreatic and hepatic injury may be associated with malignant hypertension, low flow states due to severe heart failure or post-cardiotomy, or administration of potent vasoconstrictors (Hung, Abreu Lanfranco 2014). Percutaneous mechanical thrombectomy is increasingly used for treatment of acute thrombotic events in the arterial and venous systems. There are a few case reports describing the occurrence of AP after mechanical thrombectomy (Hershberger et al. 2011).

Injury to the pancreas, because of its retroperitoneal location, is a rare occurrence, most commonly seen with penetrating injuries (gun shot or stab wounds). Post-traumatic pancreatitis is one of the complications arising from an unrecognized pancreatic duct injury. After pancreas trauma there is 10% - 17% incidence of post-traumatic pancreatitis, but the series are small (Ahmed, Vernick 2009, Fleming, Collier & Banting 1999, Leppaniemi et al. 1988).

Autoimmune pancreatitis is a rare form of CP, with as yet undetermined incidence and prevalence in the general population. Two separate subtypes have been identified: type 1 autoimmune pancreatitis and even less common type 2 autoimmune pancreatitis. Type 1 autoimmune pancreatitis has a rare presentation of AP and its sequelae. Type 2 autoimmune pancreatitis can present with features of AP or CP (O’Reilly et al. 2014).

In some patients autoimmune diseases, systemic lupus erythematosus, Sjogren’s syndrome, inflammatory bowel disease and, rarely, rheumatoid arthritis or polyarthritis nodosa-have been associated with acute pancreatitis. This etiology is uncommon and the association is complicated by the frequent ingestion of drugs, such as azathioprine or steroids, which have the potential to lead to pancreatitis in their own right (Sakorafas, Tsiotou 2000, Chang et al. 2015).

Toxins, most importantly ethanol ingestion, are the most common cause of pancreatitis around the world. Much more toxic methanol could have a direct toxic effect on the pancreas, although antidotal treatment with ethanol or prior chronic ethanol abuse may be contributing factors (Hantson, Mahieu 2000).

A careful diagnostic algorithm including routine work-up for biliary etiology (e.g. repeated right upper quadrant ultrasonography, endoscopic ultrasonography) is recommended as the first step to assess for occult microlithiasis, neoplasms and CP. If endoscopic ultrasonography is negative, (secretin-stimulated) magnetic resonance cholangiopancreatography (MRCP) is advised as a second step to identify rare morphologic abnormalities. CT of the abdomen should be performed. In spite of extensive systematic investigations and exhaustive efforts, there will be patients with true IP. If the
etiology remains unidentified, especially after a second attack of IP, genetic counseling (not necessarily genetic testing) should be considered (Working Group IAP/APA Acute Pancreatitis Guidelines 2013).

The incidence of true IP is declining as knowledge and technology advances. Thorough workup of these cases should reveal an etiology in up to 80% of cases. There are still many controversies surrounding some of the IP etiologies and full consensus agreement is lacking in many areas (Lee, Enns 2007).

2.5 Treatments of acute recurrent idiopathic pancreatitis

Because occult bile stone disease and sphincter of Oddi dysfunction account for the majority of cases of pancreatitis without a known cause, cholecystectomy, and eventually endoscopic biliary or pancreatic sphincterotomy are curative in most of cases. Endoscopic biliary sphincterotomy appeared to be a curative procedure per se in about 80% of patients. Ursodeoxycholic acid oral treatment alone has also been reported effective for treatment of biliary sludge. In uncertain cases toxin botulin injection may help in identifying some sphincter of Oddi dysfunction, but this treatment is not widely used (Testoni 2014). There are no evidence-based studies performed so far for the best treatment of IP.

2.6 The etiology of cholelithiasis

Gallstones have been recognized long in antiquity, being identified in autopsy studies of Egyptian mummies (1550-1292 BC). Gallstones are common and a significant health problem in developed societies. The prevalence of gallbladder disease including cholelithiasis is increasing, possibly as a result of the aging population, obesity, and altered lifestyle, including nutritional factors and reduced physical activity (Schwarz et al. 2007). The highest prevalence of cholelithiasis occurs in North American Indians, reaching 73% in female Pima Indians over the age of 30 years. Gallstone prevalence is 10% to 15% in white adults in developed countries. The frequency is reduced in black Americans and East Asians and it is rare in sub-Saharan Africa (Stinton, Shaffer 2012).

The majority of the patients with gallstones will never experience biliary pain or complications such as acute cholecystitis, cholangitis, or pancreatitis. The mortality rate for gallstone disease is relatively low at 0.6%. Case fatality rates have fallen >50% between the years 1979 and 2004. This decline represents the greatest decrease for any digestive disease. Although the mortality rate is quite low, the high burden of disease imposes troubling mortality figures. Gallstone disease per se also carries inherent risks. Prospective population-based surveys have revealed an increased overall mortality,
particularly from cardiovascular disease and cancer, as seen in Americans and Pima Indians with cholelithiasis (Stinton, Shaffer 2012).

Gallstones are made up of cholesterol or black or brown pigment. About 80–85% of gallstones consist predominantly of cholesterol crystals, while 15% consist of black pigment. Cholesterol and black pigment stones form in the gallbladder. When they cause symptoms, some 10% secondarily migrate from the gallbladder into the bile ducts. Brown pigment stones are the predominant type in East Asia. Brown pigment stones are associated with infections of the biliary tract, and may account in part for the high prevalence of hepatolithiasis in the intrahepatic bile ducts (Shaffer 2006, Marschall, Einarsson 2007). Approximately 60%-80% of patients with gallstones are completely asymptomatic and stones are frequently found during routine abdominal ultrasonography. Cholesterol gallstone formation is multifactorial, in which both genetic and environmental factors have roles in its pathogenesis:

Family history and genetics

In several studies there has been 2 to 3 times higher likelihood of gallstone diseases among first-degree relatives. Epidemiologic studies and the increased risk of a positive family history of gallbladder disease in a first-degree relative suggest a role of genetic factors for gallbladder disease. Genetic factors are responsible for at least 30% of symptomatic gallstone disease (Nakeeb et al. 2002). Recent genome-wide studies have provided insight into the pathogenesis of gallstones. A lithogenic variant in the gene that encodes the hepatobiliary transporter has been identified as a risk factor for gallstone disease; this variant has been associated with altered cholesterol excretion and metabolism (Hirschfield et al. 2013). Numerous candidate gallstone genes have been identified. At least 23 have been described in mouse models, all contributing to the regulation of synthesis, uptake, and secretion of hepatobiliary lipids. Of these, 15 have been identified in humans (Svensson, Makin 2012).

Age

The highest prevalence rate of gallstones was observed in women between 70 and 79 years of age: 57% had either a history of cholecystectomy or current sonographic evidence for gallstones. Symptoms and severe complications ensue in more than 40% of patients above the age of 40 years. Acute complications, as cholecystitis, cholangitis and pancreatitis, develop in 0.1–0.3% of asymptomatic stone carriers per year. The risk of cholecystitis is higher in patients with large solitary stones, whereas the risk of pancreatitis is higher in patients with small multiple stones and preserved gallbladder motility. Most patients with acute cholecystitis have an obstruction of the cystic duct (Gurusamy, Davidson 2014).
Gender

One of the most important risk factors is female gender. Rates of gallstones are two to three times higher among women than men. Pregnancy is also a major risk factor for gallstone formation. The risk is related to the number of pregnancies (Novacek 2006).

Obesity

Obesity is a well-documented risk factor, especially in women, where the risk of gallstones increases linearly with rising body weight (Friedrich et al. 2009). Several factors may contribute to the increased risk of cholesterol gallstones in obese persons. Increased hepatic secretion of cholesterol is an important feature in obesity. Impaired gallbladder motility is often a feature of obese subjects and might act as a contributing factor for the aggregation of solid cholesterol crystals and stone growth (Bonfrate et al. 2014). A cohort study in a large UK population found that each unit of BMI significantly increased the risk of symptomatic gallstones by 8% in both men and women. A BMI greater than 25 kg/m² more than doubled the risk compared with a BMI less than 25 kg/m² (Banim et al. 2011).

Rapid weight loss and bariatric surgery

The risk of developing gallstones increases in obese patients undergoing rapid weight loss either by a very low calorie diet or by bariatric surgery. The lithogenic effect of rapid weight loss is seen as early as four weeks although it generally appears within 7–18 months. Rapid weight loss (i.e., more than 1.5 kg/week) and very low calorie diet (containing <800 kcal per day) are associated with increased gallstones development in 30% to 71% of such persons. The risk of developing gallstones is particularly high (48%) when weight loss is greater than 25% of original weight (Bonfrate et al. 2014). Bariatric surgery results in substantial sustained weight loss and major improvements in glycemic control in severely obese individuals with type 2 diabetes. The most popular procedure, Roux-en-Y gastric bypass, is a lithogenic risk factor (Bonfrate et al. 2014).

Diet

Diets supplemented with cholesterol have been shown to produce lithogenic bile and gallstones in experimental animals, but studies in human subjects have yielded conflicting results. Energy intake related to obesity and energy storage represents an important risk factor for the formation of gallstones, presumably through hyperinsulinism. Of the specific dietary constituents, consumption of simple sugars and saturated fat has consistently been found associated with a higher risk of gallstones (Cuevas et al. 2004).

Total parenteral nutrition in the intensive care unit is a well-known risk factor for developing microlithiasis. The percentage of sludge-positive patients during parenteral nutrition increased to 50% between the fourth and the sixth weeks and reached 100% in
patients receiving i.v. nutritional therapy for more than 6 weeks. After the parenteral nutrition period sludge positivity decreased from 88% during the first week and to 0% by the end of the fourth week (Angelico, Della Guardia 2000).

Physical activity

Exercise reduces plasma triglycerides and insulin levels, both of which lead to a lower cholesterol saturation of the bile. Exercise increases high-density lipoprotein, which is important for reducing the lithogenicity of the bile. Exercise has also a prokinetic effect on the gut, including increasing cholecystokinin levels, which stimulates gallbladder contractility and prevents bile stasis. A British prospective study including 25 639 participants found that the physical activity was associated with a statistically significant 70% decreased risk of developing symptomatic gallstones at 5 years (Banim et al. 2010).

Underlying chronic diseases

There are many diseases that have been identified as being associated with gallstones: Advanced cirrhosis is a well-established risk factor for gallstones (black pigment stones) with an overall prevalence at 25% to 30% (Stinton, Myers & Shaffer 2010). There is a two to three fold-increased risk of developing gallstones in patients with extensive ileal Crohn's disease. In cystic fibrosis, a genetic disease leading to cirrhosis and decompensated liver failure, the prevalence of gallstones is 10% to 30%. In sickle cell disease, chronic hemolysis leads to small gallstones (Stinton, Shaffer 2012). The incidence has been reported as high as 50% by the age of 18 years. Other hemolytic diseases such as thalassemia, and hereditary spherocytosis are also cause cholecystolithiasis. Spinal cord injury is associated with a three-fold increase in gallstone formation. The incidence of gallstone formation is a common complication in patients after gastrectomy for cancer (vagotomy) and its prevalence is reported to be 15–25% higher than in the general population (Stinton, Shaffer 2012, Goldman, Pranikoff 2011, Kobelska-Dubiel, Klincewicz & Cichy 2014, Miftode et al. 2014). Hypothyroidism has been shown to induce pancreatitis only in an animal study (Rodriguez-Castelan et al. 2015).

Gallbladder motility

The estimated prevalence of gallbladder dyskinesia is about 8% in men and 21% to 22% in women. Gallbladder dyskinesia is a functional disorder of the gallbladder. The major pathophysiology of the gallbladder dyskinesia resides in the impaired emptying of gallbladder. There may be kinking, fibrosis, and thickening of the wall, and narrowing of the lumen of the cystic duct after cholecystitis for example. Impaired intrinsic (genetic?) gallbladder motility may also be one reason for gallbladder dyskinesia. Some patients with acalculous biliary-type pain may also have visceral hyperalgesia. Intra-abdominal adhesions may also hinder normal contractions of the gallbladder.
The diagnosis is difficult and depends on several factors: the presence of typical episodic (not continuous) gallbladder/biliary pain and lack of evidence of other intra-abdominal pathology. In addition, the diagnosis requires positive finding of reduced gallbladder ejection fraction on cholecystokinin-stimulated cholescintigraphy. Relief of symptoms (≥12 months) after cholecystectomy confirms the diagnosis (Francis, Baillie 2011, Dave et al. 2015).

The patients with severe symptoms and an impaired ejection fraction (EF <=35%) of the gallbladder in cholescintigraphy should be considered for laparoscopic cholecystectomy, although there is not a wide consensus on that (Paajanen et al. 2009).

2.6.1 Treatment of gallstones

Carl Langenbuch successfully performed the first cholecystectomy in 1882 (van Gulik 1986). If biliary pain or complications are present, cholecystectomy is the choice of treatment. Today the golden standard is laparoscopic cholecystectomy (LC), although indications for open surgery still exist: patients unable to tolerate a pneumoperitoneum due to hemodynamic instability or significant cardio-pulmonary comorbidity, suspicion of a gallbladder malignancy to avoid gallbladder perforation or intraperitoneal dissemination of cancer cells, patients with other intra-abdominal pathology, making a laparoscopic procedure difficult or impossible, and Mirizzi syndrome. Type I Mirizzi syndrome, consisting of extrinsic compression of the hepatic duct, can be treated laparoscopically by an experienced surgeon. Type II Mirizzi syndrome, consisting of a cholecystobiliary fistula, is a clear indication for an open procedure (van Dijk et al. 2014).

Early operation in cholecystitis decreases overall hospital stay and avoids increased complications, conversion to open procedures and mortality (Knab, Boller & Mahvi 2014). Younger patients prefer cholecystectomy whereas elderly patients with many diseases are maybe less in need of surgery (Schmidt et al. 2012).

Between 10% and 18% of patients undergoing cholecystectomy have common bile duct stones. Treatment of the bile duct stones can be conducted as open cholecystectomy plus open common bile duct exploration, laparoscopic cholecystectomy plus laparoscopic common bile duct exploration, or ERCP pre- or post-cholecystectomy in two stages (Dasari et al. 2013). The choice of the best management is often led by the local presence of professional expertise and resources, rather than by a real superiority of one strategy over another (Bencini et al. 2014, van Dijk et al. 2014). The range of conversion rates is normally less than 10%, but in acute cholecystitis it is up to 40%. Reasons to convert to open procedure include a need for better visualization of the anatomy due to inflammation, anatomic difficulty (obesity, anatomical variants), uncontrollable bleeding, limited surgical experience or significant adhesions (van Dijk et al. 2014, Paajanen et al. 2012).
2.7 Adverse drug reactions

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem (Sewal, Saini & Medhi 2015). The most common classification of ADRs is that which identifies reactions that are dose related (type A) or non-dose related (type B). Type A ADRs are usually augmented effects of the drug action. This type of reaction is common and not normally life-threatening. Type B reactions are bizarre, and not readily predicted from the pharmacological action of the drug. Type B reactions are rare and more likely to be life threatening (Atuah, Hughes & Pirmohamed 2004). Type A ADRs are predictable, reversible, and usually can be managed by lowering the dose of the offending drug. Type B ADRs are termed idiosyncratic and unrelated to the main pharmacological action of the drug, often initiated by metabolites of the parent drug or by other indirect mechanisms (Egan 2011). Types C, D and E are not mechanisms, but characteristics of their manifestations; they are not referred to frequently in the literature. The letter C refers to continuous, chronic. Type D refers to delayed in appearance, making them difficult to diagnose. Type E refers to end of use (Cobert, Cobert 2012).

2.8 Statins

Intestinal cholesterol absorption, cholesterol uptake and de novo cholesterol biosynthesis in the liver, biliary output, and its conversion to various products such as bile acids (BAs) and steroid hormones are the main steps governing cholesterol homeostasis in humans. Synthesis of BA is a major pathway of elimination of cholesterol from the body.

The small intestine plays a key role in both dietary and biliary cholesterol absorption. The reabsorbed biliary cholesterol by the small intestine is delivered to the liver by the enterolymphatic circulation. Under basal steady conditions, the main source of biliary cholesterol is high-density lipoprotein (HDL) cholesterol (Di Ciaula et al. 2014). Hypercholesterolemia is an important risk factor for atherosclerosis, which is the most common cause of death in developed countries. Statins are used to treat dyslipidemia, which prevents cardiovascular or cerebrovascular events. Statins are among the most widely used medications in the Western world and up to 200 million people take statin daily worldwide, including over 30 million people in the United States alone (Patel et al. 2014, Squizzato et al. 2011, Blaha, Martin 2013).

As in other Western societies, statin use in Finland has increased exponentially: there was an 11-fold increase in statin use between 1995 and 2000 (Ruokoniemi et al. 2008). According to the reimbursement register data of the Social Insurance Institute of Finland (population 5.2 million); approximately 660,000 individuals purchased statins in 2012, which is 12% of the population.
The use of these drugs for secondary prevention of cardiovascular disease (CVD) is well founded, but their expanding use in primary prevention in individuals without documented CVD is not always justified. Evidence suggests that in primary prevention, statins substantially decrease CVD morbidity, but only moderately reduce CVD mortality (Taylor et al. 2013). Long-term statin use might cause adverse effects, such as incident diabetes mellitus (Cederberg et al. 2015). The cost-effectiveness of such a strategy is unclear (Reiner 2013).

Statins are competitive inhibitors of the microsomal enzyme 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, which enzyme converts HMG-CoA into mevalonate, the precursor of cholesterol. The reduction in plasma low-density lipoprotein cholesterol levels following statin treatment is accounted for by varying degrees of both reductions in the production rate and increases in the fractional catabolic rate (Lamon-Fava 2013). Statins are highly effective in reducing LDL (low-density lipoprotein) and modestly effective in raising HDL. Triglyceride lowering is directly proportional to the baseline triglyceride level and to the LDL-lowering potency of the drug. Triglyceride lowering is directly proportional to the baseline triglyceride level and to the LDL-lowering potency of the drug, but is in general quite modest in this regard (Maron, Fazio & Linton 2000).

Seven statins are currently available for clinical use: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin (Chauvin et al. 2013). In Finland pitavastatin is not available.

Table 2. Statins in Finland (Pharmaceutical Information Center, Helsinki 2015).

<table>
<thead>
<tr>
<th>Statin</th>
<th>Pharmaceutical sales names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>ATORVARATIO RATIOPHARM, ATORVASTATIN ORION, ATORVASTATIN PFIZER, LIPICTOR PFIZER, ORBEOS PFIZER, ATOBIR, ATORVASTATIN BLUEFISH, ATORVASTATIN KRKA, ATORVASTATIN SANDOZ</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>FLUVASTATIN ACTAVIS, FLUVASTATIN MYLAN, FLUVASTATIN SANDOZ, LESCOL, LESCOL DEPOT NOVARTIS,</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>LOVASTATIN RATIOPHARM, LOVASTATIN STADA</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>PRAVASTATIN ORION, PRAVASTATIN RATIOPHARM, PRAVASTATIN SANDOZT</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>CRESTOR ASTRAZENECA, ROSUVASTATIN ACTAVIS, ROSUVASTATIN MYLAN, ROSUVASTATIN TEVA, ROSUVASTATIN KRKA, ROSUVASTATIN SANDOZ</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>LIPICUT SANDOZ, SIMVASTATATIN ACTAVIS, SIMVASTATIN ORION, SIMVASTATIN RATIOPHARM, ZOCOR MSD, SIMVASTATIN KRKA, SIMVASTATIN BLUEFISH</td>
</tr>
<tr>
<td>Ezetimibe+</td>
<td>INEGY MSD</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>INEGY MSD</td>
</tr>
</tbody>
</table>
Lovastatin (1987) was the first HMG-CoA reductase inhibitor and it is still widely in use. Lovastatin is found naturally in red yeast rice (Childress et al. 2013, McKenney 1988).

Simvastatin, the second statin introduced after lovastatin, is a semisynthetic derivative of lovastatin. Simvastatin is one of the best-studied statins, like lovastatin, and it is most prescribed statin in Finland. It is available without a prescription in the UK at the 10 mg dosage level (Pedersen, Tobert 2004).

Atorvastatin is one of the most widely prescribed drugs and the most widely prescribed statin in the world (Adams, Tsang & Wright 2012). Fluvastatin was the first totally synthetic HMG-CoA reductase inhibitor. Fluvastatin exhibits a favorable safety profile in comparison to other statins since cytochrome P450 enzymes do not metabolize it. However fluvastatin is a less potent cholesterol-lowering agent than newer statins (McDonald, Jardine 2008).

Rosuvastatin and pitavastatin are the two most recently developed statins. Their disposition does not depend on or is only marginally influenced by cytochrome P450 enzymes, thus potentially reducing the risk of drug-drug interactions (Hu, Tomlinson 2014). Rosuvastatin is one of the most potent statins, threefold more potent than atorvastatin, and is currently widely in use. The effect of rosuvastatin is linearly dependent on dose (Adams, Sekhon & Wright 2014). Pitavastatin is even more effective than Rosuvastatin (Ginsberg 2013).

Long-term use of statins decreases CHD mortality (Haukka et al. 2012, Taylor et al. 2013). According to 2014 published systematic review and meta-analysis of statin side effects, there was a markedly increased risk of myopathy and raised liver enzymes and weak evidence of an increased risk of type 2 diabetes mellitus (Macedo et al. 2014a). In a fresh Finnish population-based cohort study patients who used statins had a 46 % increased risk of type 2 diabetes (Cederberg et al. 2015). Preiss et al. performed a meta-analysis comparing intensive-dose and moderate-dose stains. Their meta-analysis included 32 752 individuals pooled from 5 randomized studies, the incidence of new-onset diabetes mellitus was 8.8% in the intensive-dose group versus 8.0% in the moderate-dose group. The mean follow up was 4.9 years (Preiss et al. 2011).

Statins cause an increase in the incidence of myalgias and severe myopathy. Muscle toxicity often occurs in the setting of very high dose statins that are no longer recommended (simvastatin 80 mg) or in the presence of drugs that are known to interact with statins - for example, fibrates such as gemfibrozil (Desai, Martin & Blumenthal 2014). Statins decrease mitochondrial function and alter muscle protein degradation, providing a possible pathophysiological link between statins and muscle symptoms (Stroes et al. 2015).

Statins have also been also associated with lower risks of dementia and cognitive impairment, venous thrombo-embolism, fractures and pneumonia, but these findings
were attenuated in analyses restricted to higher quality studies. Marked heterogeneity of effects across studies was also seen (Macedo et al. 2014b). The risk of pancreatitis was not evaluated in this meta-analysis.

Recent advances in pharmacogenomics have found variants of candidate genes that affect statin efficacy and safety. For one of these candidate genes, *SLCO1B1*, gene based dosing recommendations for simvastatin are now in place and genetic testing is available in some countries. Whether this will become part of routine practice to guide individual statin therapy remains to be seen, pharmacogenomics studies continues (Gelissen, McLachlan 2014).

### 2.8.1 Statins and pancreatitis

Many drugs, in particular, lipid-lowering agents, have been associated with pancreatitis. Statins have been increasingly reported as a cause of AP (Etienne, Reda 2014). But also protective effect has been reported (Thisted et al. 2006, Preiss et al. 2012).

The first case report of possible lovastatin-induced pancreatitis was published in 1989, even though they were not able to rule out penetrating ulcer (Pluhar 1989). The first observational study on the association of statins and pancreatitis was carried out by Lancashire et al. (2003). They used information held in the UK General Practitioner Research Database to compare risks for different drugs for which reports of pancreatitis were common or uncommon. They commend in the text on drugs other than statins, but in their table there was a positive association between statin use and pancreatitis. The number of patients was small (Lancashire, Cheng & Langman 2003).

In 2006 Thisted et al. carried out a case-control study on statins and pancreatitis including 2576 Danish AP patients and 25817 controls. They found that users of statins had an increased risk of AP compared with non-users, while no increased risk was found among new users. They concluded that the risk of pancreatitis induced through statin use is rather low since they found indications of an inverse association between the number of filled prescriptions for statins and risk of AP (Thisted et al. 2006).

In 2006 Singh et al. published a systematic review of case reports and they included those two observational studies on statins and pancreatitis. There were 20 published case reports and 33 spontaneous reports from the Canadian Adverse Drug Event Monitoring System database. Data were pooled together in a meta-analysis. They found that statin-induced pancreatitis can occur at any time, but seems to be very uncommon early on and more likely to occur after many months of therapy. There did not appear to be a cumulative dose effect (Singh, Loke 2006).
In 2012 Preiss et al. carried out a meta-analysis on the effects of statin therapy or fibrate therapy on pancreatitis including 16 randomized controlled cardiovascular end-point trials. There were 113,800 participants and mean follow-up was 4.1 (SD, 1.5) years. For dose-comparison analyses there were 39,614 participants. Mean follow up was over 4.8 (SD, 1.7) years. They found that statin use was associated with a reduced risk of pancreatitis in patients with normal or mildly elevated triglyceride levels. This study also suggested a possible protective effect of statins, citing both the reduction of bile cholesterol levels and reduced risk of gallstone formation in statin users as corroborating evidence (Preiss et al. 2012). In 2013 a small prospective cohort study that included 92 statin using patients with acute pancreatitis found that statin treatment reduced morbidity and mortality in acute pancreatitis (Gornik et al. 2013).

Lack of consensus regarding the precise causal link between statin use and the development of acute pancreatitis still exists (Etienne, Reda 2014). Statin-induced inflammation of the pancreas is still not well defined in the literature; also an immune-mediated inflammatory reaction, direct cellular toxicity and metabolic effects have been speculated (Johnson, Loomis 2006). There are very few studies on the role of statins in CP. One animal study with rats showed that pravastatin attenuates progression of chronic pancreatitis via its anti-inflammatory and antioxidative properties as inflammation and oxidative stress have been implicated in the pathophysiology of chronic pancreatitis (Wei et al. 2011).

2.8.2 Statins and gallstones

It has been shown that bile is desaturated of cholesterol after the long-term administration of statins (Tsai et al. 2009, Wang et al. 2013). Precipitation of excess cholesterol in bile as solid crystals is a prerequisite for cholesterol gallstone formation (Portincasa, Moschetta & Palasciano 2006). It is therefore possible that the risk of cholesterol gallstone formation is reduced during statin therapy (Kan et al. 2014).

There may be several mechanisms of statins can be used to prevent gallstone disease. First, statins are competitive inhibitors of HMG-CoA reductase, the rate and the rate-limiting enzyme in the hepatic cholesterol biosynthesis. Occupying a portion of the binding site of HMG reductase, statins block access of this substrate to the active site on the enzyme leading to a reduction of intrahepatic cholesterol production and alterations of bile cholesterol saturation. Another possible mechanism of the action of statins on gallstone disease is inhibition of cholesterol crystal nucleation (Kan et al. 2014). A long-term study in prairie dogs found that lovastatin alters biliary lipid composition and induced total dissolution of gallstones (Abedin et al. 2002).

However, most human studies have not found that statin monotherapy would leads to the complete dissolution of gallstones (Wang et al. 2013). In a French cross-sectional study and
Chinese case-control study statins were not associated with a protective effect (Caroli-Bosc et al. 2001, Chiu et al. 2012). Bodmer et al. performed a population-based case control study using a UK-based database of approximately 5 million patients to investigate statins and the reduced risk of gallstone disease. In this large observational study, a lower incidence of cholecystectomy was noted in patients taking statins (Bodmer et al. 2009). A similar finding was reported in an Israeli case-control study (Merzon et al. 2010). In a large retrospective cohort study among 2479 American women who had histories of gallstones statin use was associated with a reduced risk of cholecystectomy (Tsai et al. 2009). In a Danish population-based case control study with 357,419 participants statin users had a decreased risk for gallstone disease compared with nonusers (Erichsen et al. 2011). A population-based cohort study (between 1995 and 2009) found a declining cholecystectomy rate during the era of statins in Finland (Suuronen et al. 2013).

The relationship between statins and symptomatic gallstone disease is controversial, even thought several studies have reported a significant reduction in the incidence of symptomatic gallstones disease in patients using statin therapy (Cariati, Piromalli 2012). A 2014 meta-analysis pooled six previous studies including a large number of patients (622,868) and found that there is evidence that current statin use lowers the risk of gallstone disease compared with non-use, especially for cholecystectomy due to gallstone disease. They concluded that a major shortcoming of the studies was limited control of confounders like diet, exercise or socioeconomic status because gallstone disease is multifactorial. These studies also lacked long-term evaluation (Kan et al. 2014).

Table 3. Studies on statin use and the risk of gallstone disease (Kan et al. 2014).

<table>
<thead>
<tr>
<th>Author, year of Publication</th>
<th>Country</th>
<th>Study design</th>
<th>No of participants</th>
<th>Conclusion of the study, statin use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caroli-Bosc et al., 2001</td>
<td>France</td>
<td>Cross-sectional study</td>
<td>830</td>
<td>not associated with a protective effect</td>
</tr>
<tr>
<td>Tsai et al., 2009</td>
<td>USA</td>
<td>Prospective cohort study</td>
<td>121,700</td>
<td>reduced the risk of cholecystectomy in women</td>
</tr>
<tr>
<td>Bodmer et al., 2009</td>
<td>UK</td>
<td>Population-based case-control study</td>
<td>133,566</td>
<td>reduced the risk of cholecystectomy</td>
</tr>
<tr>
<td>Merzon et al., 2010</td>
<td>Israel</td>
<td>Population-based case-control study</td>
<td>7,325</td>
<td>reduced the risk of cholecystectomy</td>
</tr>
<tr>
<td>Erichsen et al., 2011</td>
<td>Denmark</td>
<td>Population-based case-control study</td>
<td>357,419</td>
<td>associated with a protective effect</td>
</tr>
<tr>
<td>Chiu et al., 2012</td>
<td>China</td>
<td>Population-based case-control study</td>
<td>2,028</td>
<td>not associated with a protective effect</td>
</tr>
<tr>
<td>Kan et al., 2014</td>
<td>China</td>
<td>Meta-analysis of these studies</td>
<td>622,868</td>
<td>associated with a protective effect</td>
</tr>
</tbody>
</table>
3 Aims of the study

Both gallstone disease and statin medications are common in Western countries. The relationship between statins and symptomatic gallstone disease is conflicting. It is also not known if statin therapy is common in patients with idiopathic acute pancreatitis. Very little is known about the effects of statins on the outcomes of patients treated for gallstones or pancreatitis. It is also not known if laparoscopic cholecystectomy could prevent recurrent attacks of acute idiopathic pancreatitis. The aims of this study were:

1. To study the relationship between statin use and outcome of acute pancreatitis (I).
2. To examine whether statin use modifies the severity of symptomatic gallstone disease and its treatment (II).
3. To examine the association between statin use and the risk of acute pancreatitis in the Finnish population (III).
4. To examine whether laparoscopic cholecystectomy can prevent recurrent attacks of acute idiopathic pancreatitis (IV).
4 Patients and methods

4.1 Patients

In this series of studies there were three different patient groups. Patients in study II were formed from patients in study I. Study III and IV include separate patients groups.

The total number of patients in the study III was 4,376 cases hospitalized in 2008–2010 for non-biliary non-alcohol-induced acute pancreatitis and in study IV 85 IAP patients in 8 hospitals in Finland between January 2009 and January 2013. There were 874 patients operated for gallstones in this study. In all, 3,415 patients used statins.

4.2 Methods

Study I
This retrospective cohort study included a total of 461 admissions of patients with AP and 1140 patients with gallstones in Kuopio University Hospital between 2008 and 2010. The hospital serves an area of 243,000 inhabitants. The numbers of discharge diagnoses of AP (International Statistical Classification of Diseases, 10th Revision, K85-K86) and cholelithiasis (International Statistical Classification of Diseases, 10th Revision, K80, K81, K82, K83) were obtained from the patient records. Statin use and other medication, patient comorbidities including diabetes, operative data (elective vs. emergency operation, complications), hospital stay, intensive care treatment, and mortality were recorded. All lipid-lowering drugs including statins and ezetimibe with daily doses were recorded. All known risk factors for AP and particularly statin use in idiopathic AP were analyzed.

Study II
This case-control study included 272 of those 1,140 patients with symptomatic cholelithiasis who had statin therapy. The age- and sex-matched controls (n = 272) were randomly selected from the study I cohort of patients without statin therapy. More specific data was collected: the baseline characteristics of the patients, need and type of surgical treatment, duration of operation, perioperative bleeding, postoperative complications and overall mortality rate were compared statistically between statin users and those, who have not statin in use.

Study III
This was a Fimea register-based case–control study with density sampling of the adult population of Finland in 2008–2010, approximately 4.3 million persons. There were 4,376 patients hospitalized in 2008–2010 for non-biliary non-alcohol-induced acute pancreatitis and five and 19,859 randomly selected age and sex-matched population-based controls.
Statin use between 1 January 2004 and the index date determined by the date of hospitalization for acute pancreatitis among the cases. 826 (19%) cases and 2,589 (13%) controls had been exposed to statins. The rate ratios were adjusted for comorbidities.

Data were obtained from nationwide, population-based registers from the National Discharge Register maintained by the National Institute for Health and Welfare and the Finnish Social Insurance Institution. The social security numbers of all study participants were replaced with user-specific identification codes before the data were handed over to the research team. Eight hundred and twenty-six (19%) cases had been exposed to statins, out of whom three quarters were current and one-quarter former users, whereas among 2,589 (13%) controls exposed to statins, four-fifths were current and one-fifth former users. There were no differences between the cases and the controls in the median time of exposure to statins.

**Study IV**

This randomized, prospective study was conducted between January 2009 and January 2013 and included 85 IAP patients in 8 hospitals in Finland. The diagnosis of IAP was based on the exclusion of common etiological reasons for AP, where after the patients were randomized into conservative watchful waiting (controls n=46) or LC group (n=39). During a median follow-up of 36 (5-58) months all recurrent attacks of AP after an initial IAP episode were registered.

**Table 4.** Patient characteristics in studies I-IV.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1601</td>
<td>544</td>
<td>24,235</td>
<td>85</td>
</tr>
<tr>
<td>Male/female</td>
<td>724/877</td>
<td>280/264</td>
<td>14,369/9,866</td>
<td>52/33</td>
</tr>
<tr>
<td>Gallstone</td>
<td>1140</td>
<td>544</td>
<td>561</td>
<td>see results</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>461 (41 IAP) X</td>
<td>4,376 (IAP)</td>
<td>85 (IAP)</td>
<td></td>
</tr>
<tr>
<td>Statin</td>
<td>374</td>
<td>272</td>
<td>3,415</td>
<td>20</td>
</tr>
<tr>
<td>No statin</td>
<td>766</td>
<td>272</td>
<td>20,920</td>
<td>65</td>
</tr>
<tr>
<td>Operated</td>
<td>811</td>
<td>403 (Inc. 19 stoma)</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>LC</td>
<td>593</td>
<td>261</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Open</td>
<td>218</td>
<td>123 (Inc. 30 conversion)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
4.1 Statistics

Data were analyzed using IBM SPSS (Statistical Package for the Social Sciences) Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics Armonk, NY: IBM Corp. USA), Version 17.0 (I), 21.0 (II), 22.0 (III) and version 20.0 (IV). The statistical analyses were performed using the Student independent samples t test (I), Fisher exact test (I, IV), Mann-Whitney U test (I, II, IV), independent samples t-tests (II), χ² tests (II), logistic regression analysis (III, IV) and density sampling (III). Sensitivity analyses were carried out on current users of statins (III).
5 Results

The detailed results, tables and figures are presented in the original publications. Here we present only short summaries of the results.

Study I

Statin therapy was more frequent among patients with idiopathic pancreatitis (n = 18, 44%) than in the patients with alcohol-induced (n = 34, 13%) or biliary (n = 39, 30%) pancreatitis (P < 0.002 for overall comparison). The prognosis of AP was similar in patients using statins as those not using lipid-lowering drugs.

The patients with cholelithiasis were more often older and female than the patients with AP. Approximately every fourth patient used statins with no difference between the AP (22%) and the gallstone (24%) groups. Simvastatin and atorvastatin constituted almost 90% of all statins in both study groups. The etiology of AP was alcohol in 56% of patients, gallstones in 28% of patients, and idiopathic in 9% of patients or miscellaneous in 7% of patients. The overall mortality was higher in the AP group than in the gallstone group.

During the study years from 2008 to 2010, approximately 41,000 (17%) inhabitants from our hospital catchment area received statin therapy.

Study II

There were no significant differences between the statin users and non-users regarding surgical treatment (open vs. laparoscopic cholecystectomy). Also surgical outcome was similar in patients with or without statins, although statin users had more polypharmacy and circulatory illnesses than non-users. The mean operation time for LCC was 10% shorter for the patients with statin use than for the patients without.

The prevalence of diabetes, malignancy and neurological, psychiatric, and pulmonary diseases were similar in the both study groups. The mean BMI was similar between the groups. In the statin group, simvastatin constituted 73% and atorvastatin 13% of all statins.

Approximately 27% of patients in the statin group and 25% of patients in the non-statin group were treated conservatively. Approximately 68% of all operations were elective, and 32% were emergency procedures. Three quarters of the operations were started with laparoscopy. The mean conversion rate to open surgery was 13%.

In both study groups, open surgery was more often conducted as an emergency procedure than laparoscopic surgery. Logistic regression analysis was used to adjust for age, gender
and outcomes. The results did not differ from the unadjusted results presented. All open and converted patients remained, on average, three days longer in the hospital than the laparoscopic patients (mean 5.8 ± 5.0 and 2.6 ± 9.9, respectively, P < 0.001).

Study III

There were 826 (19%) statin users among the non-biliary non-alcohol-induced acute pancreatitis cases (out of whom three quarters were current and one quarter former users) and 2,589 (13%) statin users among the control group (four-fifths were current and one-fifth former users). Statin use was associated with an increased incidence rate of acute pancreatitis (OR 1.25, 95% CI 1.13-1.39). The incidence rate was elevated especially during the first year of use both among current and former users (OR 1.37, 95% CI 1.14-1.64, and OR 1.59, 95% CI 1.29-1.97, respectively). The overall association remained when restricting analyses to current users, to participants with no history of gallstone or alcohol-related diseases, or to participants with no comorbidities or medications other than statins. Statin use seemed to have a dose–response relationship with the incidence rate of AP, with an increased incidence at a daily dose equivalent to 20 mg or more of simvastatin. The results were somewhat more pronounced when restricting the analysis to apparently healthy participants or to diabetic patients.

Study IV

During a median follow-up of 36 (5-58) months the recurrence of IAP was significantly higher in the control group than in the LC group (14 IAP/46 controls vs. 4 IAP/39 LC, 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 LC group (13/46 vs. 4/39, p=0.026).

Although preoperative trans abdominal ultrasound was negative in all patients, 23 out of 39 patients (59%) in the LC group had small stones in gall bladder during surgery. The results of the liver function tests did not differ in patients with or without gallbladder stones found in LC. We did not perform preoperative endoscopic ultrasound in this study.

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 affect recurrences of IAP.
6 Discussion

We found that statin therapy was significantly more frequent in patients with idiopathic AP than in other known etiologies of AP and that statin use was associated with an increased risk of non-biliary non-alcohol-induced AP in Finland. We also found that the patients using statins did not have worse outcomes than the non-users after cholecystectomy or other treatment of complicated gallstone disease. Statin use did not change the outcome of AP. Finally we showed that LC can effectively prevent the recurrence of first IAP attack.

Soon after statins were introduced it was reported that the molar percent of cholesterol in human gallbladder bile decreased during lovastatin therapy, and thus lithogenic index of gallbladder bile was also reduced during lovastatin treatment (Freeman et al. 1988). This is today the most consistent evidence; bile is desaturated of cholesterol after the long-term administration of statins (Tsai et al. 2009, Wang et al. 2013). Many studies have shown that statin users have reduced risk of symptomatic gallstones and especially cholecystectomy (Bodmer et al. 2009, Tsai et al. 2009). The connection between statin use and complicated gallstone disease or pancreatitis is still vague and without of consensus. Microlithiasis is considered to cause up to one third of all cases of IP (Lee, Enns 2007).

To examine the association between statin use and the risk of AP we conducted the first study in which we collected pancreatitis patients treated in hospital and then another larger nationwide study with collaboration of Fimea. We found that the use of statins was common among patients with AP and statin use was associated with a 25% increased risk of pancreatitis. This does not indicate necessarily a causal relationship between statin use and AP, because statin users were more likely to have diabetes, obesity, and dyslipidemia.

To examine whether statin use modifies the severity and treatment of symptomatic gallstone disease we conducted a case-control study. In this study patients using statins did not have worse outcomes after cholecystectomy than the non-users, although the statin users were older, had polypharmacy and demonstrated more comorbidities than the non-users. Surprisingly statin therapy was also associated significantly with a shorter laparoscopic operation time. These findings are of clinical importance, as one would anticipate that statin users would have more postsurgical complications than non-users. The mechanism by which statins might shorten the operation time remains unknown. There is evidence that statins might have anti-inflammatory, anti-fibrotic and anti-oxidative actions (Wei et al. 2011). We anticipated that statin users would have less severe acute gallbladder inflammation, fewer stones in the common bile duct and more frequent laparoscopic cholecystectomy than non-users; this hypothesis proved wrong. Most human studies have not found that statin monotherapy leads to the complete dissolution of gallstones (Wang et al. 2013), but statins reduce bile cholesterol content, which may theoretically reduce the risk of developing microgallstones or sludge, a risk factor for AP.
The strength of our study is that it was first study to examine the relationship between statin use and operative outcome; there are no previous studies of this kind. Although studies II and I are retrospective studies, the coverage is wide: all patients with diagnoses of AP and symptomatic gallstones during 2008 and 2010 recorded at Kuopio University Hospital were included.

Our studies have some limitations. We do not know how regularly patients took the drug. Exposure is seldom continuous in real-life and intermitted drug intake is common practice. To reduce the effect of selection bias we select only exposed and unexposed patients that are comparable on key confounding factors. In studies I and II we were not able to assess the prevalence of microlithiasis in statin users because no bile samples were analyzed microscopically, and endoscopic ultrasound was not performed systematically in the patients with idiopathic AP (Saraswat et al. 2004). Furthermore, because the studies designs are cross-sectional, we cannot address the causality between statin use and AP or symptomatic gallstone disease. Due to retrospective nature of studies II, and I we could not determine whether the gallstone formation developed before the statin medication was administered. Gallstone formation occurs over a long time period. The estimated growth rate of gallstones was found to be approximately 2 mm per year and gallstones are usually asymptomatic (Cuevas et al. 2004). Furthermore, we do not have accurate data on the patients’ adherence to statin use or on the duration of the statin treatment in individual patients. Possible alcohol abuse as an etiological factor behind recurrent pancreatitis may also be difficult to confirm in a register-based study (Nordback, Sand & Andren-Sandberg 2007).

In study III, statin use was associated with an increased risk of non-biliary non-alcohol-induced acute pancreatitis. This study was a Finnish population based case-control study with incidence density sampling. The association was more apparent during the first year of statin use and among those with high doses. Our findings also suggest that there is a dose-response relationship between statins and the risk of AP: the higher the dose, the higher the risk. The results were somewhat more pronounced when restricting the analysis to apparently healthy users or diabetic patients only. The findings were similar in this study if the analyses were restricted to those with no history of gallstone or alcohol-related diseases or to current users only. This raises the questions whether statins are as safe as thought and whether use in primary prevention is always justified. AP is one of the most common causes of admission to hospital for gastrointestinal disorders. The annual incidence of AP ranges from 13 to 45 per 100,000 people (Lankisch, Apte & Banks 2015). Statin-associated myopathy, with significant elevation of serum creatine kinase (CK), is a rare, but serious side effect of statins, affecting 1 per 1000 to 1 per 10,000 people on standard statin doses (Stroes et al. 2015). As AP can be a life-threatening condition, this increased risk should be considered when assessing the risk-benefit-ratio of the use of statins, especially at higher doses and potencies and when used in primary prevention in patients without established cardiovascular disease. It may be that those patients who are extremely sensitive to statin-induced pancreatitis get it soon and long-term use may have
been connected to microlithiasis induced pancreatitis.

In a population-based study involving three Danish counties, Thisted et al. found that users of statins had an increased risk of AP compared with non-users, which is consistent with our findings. The highest risk was found among former users (those patients who had previously used statins greater than 90 days prior to hospital admission for AP), while no increased risk was found among new users. They found indications of an inverse association between the number of filled prescriptions for statins and risk of AP (Thisted et al. 2006).

In a systematic review Singh and Loke stated that the patients who used statins develop pancreatitis more frequently. Our findings are in accordance with that. Singh and Loke also concluded that statin-induced pancreatitis can occur at any time, but seemed to be very uncommon early on and more likely to occur after many months of therapy. Furthermore they suggested, contrary what we found, that there does not appear to be a cumulative dose effect and increasing age does not appear to be a major susceptibility factor, although statins are generally used more frequently in older individuals. They pointed out that there are a number of major study limitations, particularly with respect to the analysis of case reports (Singh, Loke 2006).

Contrary to above, in a meta-analysis Preiss et al. (2012) suggested that statins reduce the incidence of pancreatitis. Strengths of this meta-analysis were the large number of patients (113,800) and that the analysis was conducted using data from randomized trials. There are also limitations in this meta-analysis. Pancreatitis was not a primary endpoint in these trials, which were primarily designed to assess the effect of lipid-modifying therapy on cardiovascular events. There was lack of standardization when recording episodes of pancreatitis, which results in variation between trials. They were not able to examine specific causes of pancreatitis such as gallstones and they were unable to separate reports of pancreatitis into acute or chronic cases. They also did not have access to individual participant data, which may have reduced their ability to identify any relationship with the extent of triglyceride lowering. Because the trials tended to exclude participants with marked hypertriglyceridemia, these findings may not necessarily be generalizable to statin users in general (Preiss et al. 2012). Their report published data were available for only two of the studies (Desai, Martin & Blumenthal 2014). Our results differ from the results of the meta-analysis by Preiss et al. Our study was population-based and the sample can be considered representative of both statin users and patients with acute pancreatitis in real-world practice settings. The controls were randomly selected and matched for age and sex.

The main strengths of our nationwide study were the large sample size, the population-based design, and the ability to link different registers with prospectively collected data. The quality of the Social Insurance Institution registers, precision of records, and applicability for research purposes are considered good (Furu et al. 2010). There is some limitation in this study; we did not have access to patients’ records. Case-control analyses
are susceptible to bias by unmeasured confounders and to confounding by indication. One confounding factor is the metabolic syndrome but marked hypertriglyceridemia is a quite rare cause for pancreatitis in Finland. Furthermore, in individual cases one cannot conclude whether pancreatitis is idiopathic or statins induced.

To examine whether LC can prevent recurrent attacks of IAP we found 59% of IP patients in the LC group had small stones in the gallbladder. Therefore, they probably had microlithiasis-induced AP, not IP. LC is a safe method with minimal (0.12-0.13%) mortality, and it would thus be a justifiable treatment for IAP, when all known aetiologies have been ruled out. One interesting finding was that patients taking lipid-lowering medication had stones or microlithiasis less frequently during LC. Study IV was a prospective randomized multicentre study. It is first study with this kind of hypothesis and study design. Limitations of study were small number of patients, and we did not perform endoscopic ultrasound (EUS) to more reliably detect small gallstones or biliary sludge, since it was not available in all hospitals. We are continuing to recruit more patients and will publish a new study in the future with a larger number of patients and longer follow-up.

Statins are commonly used drugs and statins benefit millions of people. Their use has even been argued to have no excess of adverse events among people without evidence of CVD (Taylor et al. 2013). Statins are used also for primary prevention, in patients without disease and sometimes at low risk for disease. However, statins have adverse drug reactions. This is highlighted because there are so many users and some may use statins without a clear indication. Statins have been shown to influence biliary cholesterol secretion. Thus, they might represent a useful new therapeutic drug in at least Western patients with symptomatic cholesterol gallstones, and might also be able to prevent the formation of cholesterol gallstones in selected subjects at risk (Portincasa et al. 2012). On the other hand, statin use could produce more small gallstones, a well-known risk factor for acute pancreatitis. Cholelithiasis is common and usually without any symptoms. It is important to get more information on the possible harmful effects of statins and especially in patients with gallstone disease. Statins and alcohol are nowadays both widely used and they may be a harmful combination, especially in terms of acute pancreatitis. Lack of consensus regarding the precise causal link between statin use and the development of acute pancreatitis still exists. Our nation-wide study seems to indicate that statins are associated with increased risk of AP, but the possible biological mechanism by which exposure to statins could result in AP remains unknown.

Given more data on the available evidence, the association between statins and pancreatitis could be better defined through better-controlled studies. More studies are required to clarify the precise relationship between statin use and the development of acute pancreatitis.
7 Conclusions

Based on the present study the following conclusion can be drawn:

1. Patients with idiopathic acute pancreatitis use statins more often than patients with alcohol-induced or biliary pancreatitis (Study I).

2. Statin users have more often polypharmacy and circulatory illnesses than non-users but they do not have worse outcomes after cholecystectomy than non-users (Study II).

3. Patients who use statin may have an increased risk of acute pancreatitis (Study III).

4. LCC can effectively prevent the recurrence after the first IAP attack (Study IV).
8 Future perspectives

We plan to continue Study IV and recruit 250-100 patients more and publish 5-10 years results on the effect of LC in the prevention of recurrence after the first IAP attach. Since the risk of developing gallstones increases in obese patients undergoing bariatric surgery, we have planned a study where we look statin use among these patients to prevent gallstone formation in humans. With Fimea we have decided to further study the interrelationship of statin use, gallstones and pancreatitis.
9 References


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Portincasa, P., Ciaula, A.D., Bonfrate, L. & Wang, D.Q. 2012, "Therapy of gallstone disease: What it was, what it is, what it will be", *World journal of gastrointestinal pharmacology and therapeutics*, vol. 3, no. 2, pp. 7-20.


In up to 20% of acute pancreatitis the etiology is unknown and term idiopathic pancreatitis is used. We found that patients with idiopathic acute pancreatitis use statins more often than patients with alcohol or biliary pancreatitis and patients who use statins may have an increased risk of pancreatitis. We also found that many idiopathic pancreatitis patients have small gallstones, even though none were detected and recurrent acute idiopathic pancreatitis is less common after cholecystectomy.
ERRATA


3. Sivu VIII, rivi 1-2; Statiinien käyttäjillä esiintyi useammin etiologialtaan epäselvä haimatulehdus kuin sappikivitaudin tai alkoholin aiheuttama haimatulehdus:
Statiinien käyttöä esiintyi useammin etiologialtaan epäselvä haimatulehdehduksen yhteydessä kuin sappikivitaudin tai alkoholin aiheuttaman haimatulehduksen yhteydessä.


6. Page 37, row 2; recruit 250-100 patients more: 25-50