

**DRUG-INDUCED  
ACUTE PANCREATITIS**

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# Drug-induced acute pancreatitis

Acute pancreatitis door geneesmiddelen

## Proefschrift

ter verkrijging van de graad van doctor  
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op gezag van de Rector Magnificus  
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en volgens besluit van het College voor Promoties.

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## **Manuscripts based on studies presented in this thesis**

### ***Chapter 2.1***

Eland IA, Sturkenboom MCJM, Wilson JHP, Stricker BHCh. Incidence and mortality of acute pancreatitis between 1985 and 1995. *Scand J Gastroenterol* 2000;35:1110-6.

### ***Chapter 2.2***

Eland IA, Sturkenboom MCJM, van der Lei J, Wilson JHP, Stricker BHCh. Incidence of acute pancreatitis. *Scand J Gastroenterol* 2002;37:124.

### ***Chapter 3.1***

Eland IA, van Puijenbroek EP, Sturkenboom MCJM, Wilson JHP, Stricker BHCh. Drug-associated acute pancreatitis: twenty-one years of spontaneous reporting in The Netherlands. *Am J Gastroenterol* 1999;94:2417-22.

### ***Chapter 3.2***

Eland IA, Rasch MC, Sturkenboom MCJM, Bekkering FC, Brouwer JT, Delwaide J, et al. Acute pancreatitis attributed to the use of interferon  $\alpha$ -2b. *Gastroenterology* 2000;119:230-3.

### ***Chapter 3.3***

Eland IA, Sturkenboom MCJM, Biour M, Langman MJS, Wiholm B-E, Wilson JHP, et al. Drug-induced acute pancreatitis: a systematic review. Submitted.

### ***Chapter 4.1***

Eland IA, Alvarez CH, Stricker BHCh, Rodriguez LA. The risk of acute pancreatitis associated with acid-suppressing drugs. *Br J Clin Pharmacol* 2000;49:473-478.

### ***Chapter 4.2***

Eland IA for the EDIP study group. Angiotensin converting enzyme inhibitors increase the risk of acute pancreatitis: The European case-control study on drug-induced acute pancreatitis. Submitted.

### ***Chapter 4.3***

Eland IA for the EDIP study group. The risk of acute pancreatitis associated with psychotropic drugs: The European case-control study on drug-induced acute pancreatitis. Submitted.

### ***Chapter 4.4***

Eland IA for the EDIP study group. Acute pancreatitis associated with the use of

fibrates: The European case-control study on drug-induced acute pancreatitis. Submitted.

#### ***Chapter 4.5***

Eland IA for the EDIP study group. Acute pancreatitis associated with the use of vitamin D: The European case-control study on drug-induced acute pancreatitis. Submitted.



CHAPTER 1 *One*

*Introduction*



## **INTRODUCTION**

Acute pancreatitis is an inflammatory disease of the pancreas with sudden onset. The severity of acute pancreatitis may vary from mild to life threatening. There are many risk factors for acute pancreatitis, among which gallstones and alcohol abuse are most widely known. Drugs are considered as potential risk factors for acute pancreatitis, but have received relatively little attention in the medical literature.

In this thesis, several epidemiological studies were performed to assess the relationship between drug use and acute pancreatitis.

### **Outline of the thesis**

To estimate the public health impact, the incidence and mortality of acute pancreatitis were studied in chapter 2. Chapter 3 starts the exploration of the relation between drug use and acute pancreatitis with a description and evaluation of spontaneous reports on drug-associated acute pancreatitis. Next, we systematically reviewed the literature to summarise current knowledge on drug-associated acute pancreatitis. On the basis of the descriptive studies described in chapter 3, we conducted several analytic epidemiologic studies to quantify the association between use anti-ulcer drugs, cardiovascular drugs, psychotropic drugs, vitamin D, lipid lowering drugs and acute pancreatitis in chapter 4. The results of our studies on drug-associated acute pancreatitis are discussed in chapter 5.

## **ACUTE PANCREATITIS: A GENERAL OVERVIEW**

### **Introduction**

Acute pancreatitis is an acute inflammatory process of the pancreas. The clinical signs may vary from mild disease in most patients to multi-organ failure and sepsis in about 20% of patients.(1,2) In mild acute pancreatitis there is minimal tissue damage which is followed by resolution of the inflammatory process with relatively little tissue damage. In severe acute pancreatitis, the pancreas contains areas of both oedema and necrosis. Veins and venules are often affected with granulocytic infiltration, thrombosis, necrosis, rupture and haemorrhage.(3)

The overall case-fatality of acute pancreatitis is 5-10%,(4) but may be as high as 40% in patients with infected necrosis of the pancreas.(5) Early deaths in acute pancreatitis are mainly due to multi-organ failure, which is probably caused by release of mediators and cytokines from the inflamed and necrotic pancreas.(6) The majority of deaths, however, are due to local and systemic septic complications later in the

disease course.(6)

## **Clinical presentation and diagnosis**

Acute pancreatitis usually has a rapid onset of severe upper abdominal pain, nausea, vomiting, and low-grade fever. In its most typical form, the pain is located in the epigastric area, radiates to the back, and is worse in the supine position.(2) Signs of peritonitis are usually absent or mild, due to the retroperitoneal location of the pancreas. In its most severe form, acute pancreatitis may present with cardiac and renal failure, hypovolemic shock, and pulmonary insufficiency within two weeks of onset. Local complications such as pseudocysts, and pancreatic abscess usually develop later in the course of acute pancreatitis.(1)

The diagnosis of acute pancreatitis rests on careful clinical examination with supportive evidence from laboratory and radiological techniques. The association between acute pancreatitis and elevated serum levels of amylase has been recognised for decades,(7) and amylase measurement is still the most frequently used diagnostic test for acute pancreatitis. However, serum amylase is also elevated in patients with salivary gland disorders, renal failure, and intestinal perforations.(8) Serum lipase is a more specific sign of acute pancreatitis than serum amylase and remains elevated for a longer period of time.(9) Other potential markers such as phospholipase A2, pancreas-associated protein, and trypsinogen-2 have been tested, but have failed to find their way into clinical practice.(10)

Ultrasonography and computed tomography may show edema of the pancreas, pancreatic necrosis, peripancreatic fat infiltrations, fluid collections, pseudocysts, or a pancreatic abscess. However, these imaging procedures may be negative in over 30% of patients.(11,12)

## **Treatment**

Treatment of acute pancreatitis depends on on the severity. In most cases, treatment of acute pancreatitis is largely supportive and consists of eliminating oral intake, vigorous rehydration, and parenteral analgesia. Patients with a severe attack of acute pancreatitis should be admitted to an intensive care unit for optimal support. Several prognostic models have been developed to identify patients with a high risk of running a severe course (table 1a and 1b). The APACHE II score is accurate, can be assessed in the first 24 hours after admission, but is cumbersome. Many single value predictors have been tested, but most assays are not routinely available (table 2). C-reactive protein (CRP) is the most practical single value predictor, but is only accurate after 48 hours.(13) Measurement of trypsinogen activation peptide (TAP) in urine is a promising development.(14)

**Table 1a**  
**APACHE II score for severity prediction in acute pancreatitis**

	APACHE II score								
	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature (°C)	≥41	39.0-40.9							
Mean arterial BP (mmHg)	≥160	130-159	110-129						
Heart rate (bpm)	≥180	140-179	110-139						
Respiratory rate	≥50	35-49		25-34					
A-aPo2 *	≥500	350-499	200-349						
PaO2 †									
Arterial pH	≥7.7	7.6-7.69		7.5-7.59					
HCO3- ‡ (mmol/l)	≥52	41-51.9		32-40.9					
Sodium (mmol/l)	≥180	160-179	155-159	150-154	130-149				
Potassium (mmol/l)	≥7	6-6.9		5.5-5.9					
Creatinine (mg/100ml)	≥3.5	2-3.4	1.5-1.9						
Hematocrit (%)	≥60		50-59.9	46-49.9	30-45.9				
WBC count (10 <sup>9</sup> /l)	≥40		20-39.9	15-19.9	3-14.9				
Glasgow coma score		15 minus actual		Glasgow score					

APS = acute physiology score, BP = blood pressure, A-aPo2 = alveolar-arterial oxygen difference, PaO<sub>2</sub> = pressure of oxygen in arterial blood, WBC = white blood cell.

\* use if percentage of inspired oxygen (FIO<sub>2</sub>) > 50%

† use if FIO<sub>2</sub> < 50%

‡ use only if no arterial blood gas measurement is available  
double score in acute renal failure

**APACHE II score continued**

Age points (AP)	Chronic health problems (CHP)	Scoring
≤44	0	History of severe organ system insufficiency APS + AP + CHP = Total score
45-54	2	or immunocompromised:
55-64	3	Non-operative 5
65-74	5	Emergency postoperative 5
≥75	6	Elective postoperative 2

Cut-off levels differ between studies: a score of more than 6-9 points is associated with severe acute pancreatitis.

**Table 1b**  
**Glasgow criteria for severity prediction in acute pancreatitis**

Factor	Positive if
Age	> 55 years
Arterial PO2	< 8.0 kPa
serum albumin	< 32 g/l
Serum calcium	< 2.0 mmol/l
White blood cell count	> 15.10 <sup>9</sup> /l
ASAT	> 100 U/l
LDH	> 600 IU/l
Blood glucose	> 10 mmol/l (in absence of DM)
plasma urea	> 16 mmol/l

The presence of 3 or more prognostic factors is associated with severe acute pancreatitis

**Table 2**  
**Single value predictors**

Predictors
C-reactive protein (CRP) *
Tumour necrosis factor (TNF) *
Interleukin-6 *
Interleukin-8 *
Polymorphonuclear elastase *
Trypsinogen activation peptide (TAP) *
Phospholipase A <sub>2</sub> *
Pancreas-associated protein (PAP) *
Carboxypeptidase B activation peptide *
Obesity (BMI > 30 kg/m <sup>2</sup> )
Pleural effusion

\*Cut-off levels differ between studies

In severe pancreatitis, the patient requires careful monitoring for development of local and systemic complications. Shock should be treated immediately and respiratory support and dialysis are used to treat pulmonary complications and renal failure. Patients with a severe attack of acute pancreatitis should also receive nutritional support. Enteral feeding has shown to be superior to total parenteral nutrition.(15,16) Drug therapy has not proven to be successful. Amongst others, somatostatin, aprotinin, gabexate, and leixipafant have failed to ameliorate the clinical course of acute pancreatitis.(1,17) The debate on prophylactic use of antibiotics continues, but imipenem-cilastatin probably reduces the incidence of pancreatic infection in patients with pancreatic necrosis.(18)

Endoscopic retrograde cholangiopancreatography (ERCP) should be performed in patients with severe pancreatitis if biliary obstruction is suspected on the basis of hyperbilirubinemia or clinical signs of cholangitis.(18) Infected pancreatic necrosis needs urgent surgical debridement as mortality in untreated patients reaches 100%.(18) CT-guided fine needle aspiration may be needed to distinguish between sterile and infected necrosis. Percutaneous and endoscopic drainage of infected pancreatic necrosis has successfully been attempted and can be used in selected patients.(18)

## Pathogenesis

Acute pancreatitis is an autodigestive disease; i.e. the pancreas is injured by its own digestive enzymes. The pancreas synthesizes and stores its digestive enzymes as inactive pro-enzymes or zymogens. Trypsinogen is hydrolysed to trypsin and TAP by the

Table 3  
Inflammatory mediators in acute pancreatitis

Pro-inflammatory	Anti-inflammatory
Tumour necrosis factor- $\alpha$	Interleukin-10
Interleukin-1 $\beta$	C5a
Interleukin-6	
Interleukin-8	
Platelet activating factor	
C5a	
Substance P	
Intercellular adhesion molecule-1	

brush border enzyme enteropeptidase in the duodenum. Trypsin subsequently activates the remaining pro-enzymes. In acute pancreatitis there is premature, intrapancreatic activation of trypsinogen, which leads to autodigestion.(19) The mechanisms responsible for premature activation are unknown, but activation of trypsinogen as the central event in the induction of pancreatitis is exemplified by recent discoveries in hereditary pancreatitis. Mutations in the cationic trypsinogen gene (PRSS1) inhibit autolysis or promote auto-activation of trypsinogen thereby overwhelming the pancreatic defence mechanisms.(20,21) Mutations in the pancreatic secretory trypsin inhibitor gene (PSTI, SPINK1) lower the threshold for other etiological factors.(21) In experimental models, co-localisation of lysosomal enzymes, notably cathepsin B, with trypsinogen leads to activation of the latter.(19, 22) Recent evidence showed that elevated intracellular calcium levels are important in the premature activation of trypsinogen.(23)

Once zymogens are activated within the pancreas, acinar cell damage occurs which leads to a local inflammatory response. In severe acute pancreatitis, the inflammatory mediators reach the general circulation leading to a systemic inflammatory response syndrome (SIRS).(24) As a consequence, systemic leukocyte activation leads to distinct organ damage. Blockage of pro-inflammatory mediators (table 3) may potentially ameliorate acute pancreatitis, but this has only been demonstrated in experimental models.(24)

## Etiology

There are many risk factors for acute pancreatitis (table 4). However, the link between these risk factors and the above-described pathophysiological mechanisms remains unexplained. Although alcohol abuse and cholelithiasis are present in a majority of patients, only 3% of patients with gallstones and 10% of patients with alcohol abuse develop pancreatitis.(25) Reflux of bile into the pancreatic duct and stasis of pancre-

**Table 4**  
**Etiology of acute pancreatitis**

<p><b>Obstruction</b></p> <ul style="list-style-type: none"> <li>• Gallstones</li> <li>• Sludge</li> <li>• Carcinoma: pancreas, ampulla</li> </ul> <p><b>Toxins</b></p> <ul style="list-style-type: none"> <li>• Alcohol</li> <li>• Drugs</li> <li>• Others: insecticides, scorpion venom, etc.</li> </ul> <p><b>Metabolic</b></p> <ul style="list-style-type: none"> <li>• Hypercalcemia</li> <li>• Hypertriglyceridemia</li> </ul> <p><b>Trauma</b></p> <ul style="list-style-type: none"> <li>• ERCP</li> <li>• Abdominal surgery</li> <li>• Blunt abdominal trauma</li> </ul>	<p><b>Infection</b></p> <ul style="list-style-type: none"> <li>• Viral: mumps, rubella, Coxsackie, hepatitis A + B, Cytomegalo virus, Herpes simplex, Varicella zoster</li> <li>• Parasitic: Ascariasis, Cryptosporidium, Toxoplasma gondii</li> <li>• Bacterial: Mycoplasma, Campylobacter, Mycobacteria, Legionella, Leptospira</li> </ul> <p><b>Others</b></p> <ul style="list-style-type: none"> <li>• Hereditary</li> <li>• Cardiopulmonary bypass</li> <li>• Penetrating peptic ulcer</li> <li>• Pancreas divisum</li> <li>• Vasculitis</li> <li>• End stage renal failure</li> <li>• etc.</li> </ul>
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atic secretions due to obstruction have been proposed as a possible explanation for biliary pancreatitis. (26,27) Smaller stones seem to carry a higher risk of acute pancreatitis than larger stones. (28)

About 5% of patients undergoing ERCP develop clinical pancreatitis. Risk factors include female gender, prior pancreatitis, lack of experience with ERCP of the performing gastroenterologist, and difficulties in the cannulation. Hypercalcemia and hypertriglyceridemia are the most likely causes for acute pancreatitis in a few percent of all patients with acute pancreatitis. In 10-20% of patients no apparent cause for acute pancreatitis can be found.

Drugs have since long been acknowledged as a potential risk factor for acute pancreatitis. (29) Since drugs are considered a rare cause of acute pancreatitis, they are frequently overlooked as a possible cause. The Drug Safety Unit of the Dutch Inspectorate for Health Care received numerous spontaneous reports on drug-associated acute pancreatitis concerning a wide variety of drug classes. This thesis aims to describe the relationship between use of therapeutic drugs and development of acute pancreatitis.

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CHAPTER 2

*two*

*Incidence of  
acute pancreatitis*



Incidence and mortality  
of acute pancreatitis:  
hospital discharge data

*2.1*

## **Incidence and mortality of acute pancreatitis between 1985 and 1995**

**Introduction:** *The incidence of acute pancreatitis seems to have risen in Western countries. It has been suggested that this rise can be explained by improved diagnostic procedures. We performed a nationwide study to assess the annual gender and age specific incidence and mortality rates of acute pancreatitis in the Netherlands between 1985 and 1995, a period in which diagnostic procedures did not change considerably.*

**Methods:** *We conducted a population-based retrospective follow-up study, in which we used automated hospital discharge data accumulated by Prismaant Health Care Information. All patients admitted with acute pancreatitis (ICD-9CM; 577.0) in the Netherlands were identified. We accounted for referrals to other hospitals to avoid double counting and for miscoding of chronic pancreatitis as acute pancreatitis. The annual population size was retrieved from the Netherlands Central Statistics Office.*

**Results:** *The observed incidence rate of acute pancreatitis increased from 12.4/100,000 person-years (95% CI; 11.8-12.9) in 1985 to 15.9/100,000 person-years (95% CI; 15.3-16.5) in 1995. The annual mortality rate of acute pancreatitis remained fairly stable at 1.5/100,000 person-years. The incidence and mortality rate of acute pancreatitis rose considerably with age. The case-fatality proportion of first admissions for acute pancreatitis declined from 14.3% to 10.7%. The case-fatality for relapses remained stable at 3.2%.*

**Conclusions:** *In this retrospective study, the observed incidence rate of acute pancreatitis increased by 28% between 1985 and 1995. Due to a decline in the case-fatality proportion, the mortality remained stable during this period.*

## **INTRODUCTION**

Acute pancreatitis is a severe disease with a considerable mortality. Despite advanced critical care, the case-fatality remains about 5-10%.<sup>(1-4)</sup> Gall-stones and alcohol are the most important risk factors for acute pancreatitis.<sup>(5-7)</sup> Other risk factors include hyperlipidemia, hypercalcemia, ERCP and trauma. In 10 to 25% of the patients with acute pancreatitis no obvious risk factors are present.

In the past 30 years, the incidence of acute pancreatitis seems to have risen in Western countries.<sup>(1,3,8-11)</sup> However, it has been suggested that this rise in incidence of acute pancreatitis may be explained by improved diagnostic tests and imaging procedures. In order to assess the recent trends in incidence and mortality rates of acute pancreatitis, we performed a nationwide retrospective follow-up study in the Netherlands between 1985 and 1995.

## **METHODS**

### **Setting**

Prismant Health Care Information maintains the National Information System on Hospital Care (NISHC). The NISHC is a nationwide, automated database, which collects anonymized data on all hospitalizations in academic and general hospitals in the Netherlands. Recorded data include gender, date of birth, place of residence, type of health care insurance, admission date, number of days in hospital, mortality, plus a primary discharge diagnosis and up to nine secondary discharge diagnoses, which are coded according to the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9CM). All data are verified by Prismant on a monthly and yearly basis.

### **Design and source population**

We conducted a population based retrospective follow-up study, using automated discharge hospital data, which are accumulated by Prismant. The source population comprised all inhabitants of the Netherlands between 1985 and 1995. The annual population size was retrieved from the Netherlands Central Statistics Office.

### **Case ascertainment**

Cases were defined as all persons who were admitted for acute pancreatitis between 1985 and 1995. To this purpose we identified all persons who had a primary or second-

ary diagnosis of acute or chronic pancreatitis (ICD-9CM; 577.0, 577.1) between 1980 and 1995. An identification code consisting of gender, date of birth and place of residence was assigned to each patient.

In order to avoid double counting of cases we accounted for referrals to other hospitals by checking for consecutive discharge and admission dates, and for identical discharge diagnoses within one admission. Thirty-seven admissions were notified twice to Prismaant, these second notifications were removed from the analysis.

To avoid overestimation of the incidence of acute pancreatitis due to miscoding of chronic pancreatitis, we recoded all discharge diagnoses of acute pancreatitis into chronic pancreatitis if an accompanying discharge diagnosis of chronic pancreatitis was recorded for the same admission. In addition, we recoded a discharge diagnosis of acute pancreatitis into chronic pancreatitis if the patient had a discharge diagnosis of chronic pancreatitis in the five years prior to admission.

An admission for acute pancreatitis was considered as a first admission if the patient had no history of acute pancreatitis in the five years preceding the admission.

## **Etiology**

The total yearly consumption expressed in litres of pure alcohol per capita was obtained from the Commodity Board for the Distilled Spirits Industry. (12) The number of patients admitted for gallstone diseases from 1985-1995 and the total number of endoscopic procedures to the pancreatic and bile ducts from 1991-1995 were collected from the NISHC.

## **Validation of NISHC**

In order to quantify underreporting of acute pancreatitis discharge diagnoses to Prismaant, we evaluated coded discharge information of 17 consecutive patients who were recruited for a population-based case-control study on acute pancreatitis in 1997. Inclusion criteria for this study were a clinical picture compatible with acute pancreatitis combined with a serum amylase or lipase of more than two times the upper normal limit, or a typical picture at CT, ultrasound examination, laparotomy, or autopsy.

Secondly, to check the concordance of Prismaant discharge information with the information recorded in the original medical records, we scrutinized the medical records of all patients of the University Hospital Rotterdam who were notified to Prismaant as having acute pancreatitis in 1985, 1990 and 1995. A diagnosis of acute pancreatitis was accepted when the above described case-definition was met.

## Analysis

Annual gender and age specific incidence rates were calculated using the number of cases of acute pancreatitis in the numerator and the mid-year average number of inhabitants as denominator. Incidence rates were expressed as number of cases per 100,000 person years. According to Rothman et al, 95 percent confidence intervals (95% CI) should be calculated even if an entire population is included in a study.(13) We calculated the intervals on the basis of a Poisson distribution.(14) In addition, we recalculated the annual incidence of acute pancreatitis by reference to the age and gender structure of 1985.

Mortality rates were calculated as the annual number of patients who died during admission for acute pancreatitis divided by the mid-year average number of inhabitants in each age and gender category. Ninety-five percent confidence limits were calculated on the basis of a Poisson distribution.

The case-fatality proportion was calculated as the percentage of patients with an acute pancreatitis who died during admission. Ninety-five percent confidence limits were calculated on the basis of a normal approximation to the binomial distribution.

The correlation between the incidence of gallstone diseases, the incidence of endoscopic procedures to the pancreatic and bile ducts, the amount of alcohol consumed and the incidence of acute pancreatitis was calculated using Spearman's correlation coefficient ( $r_s$ ).

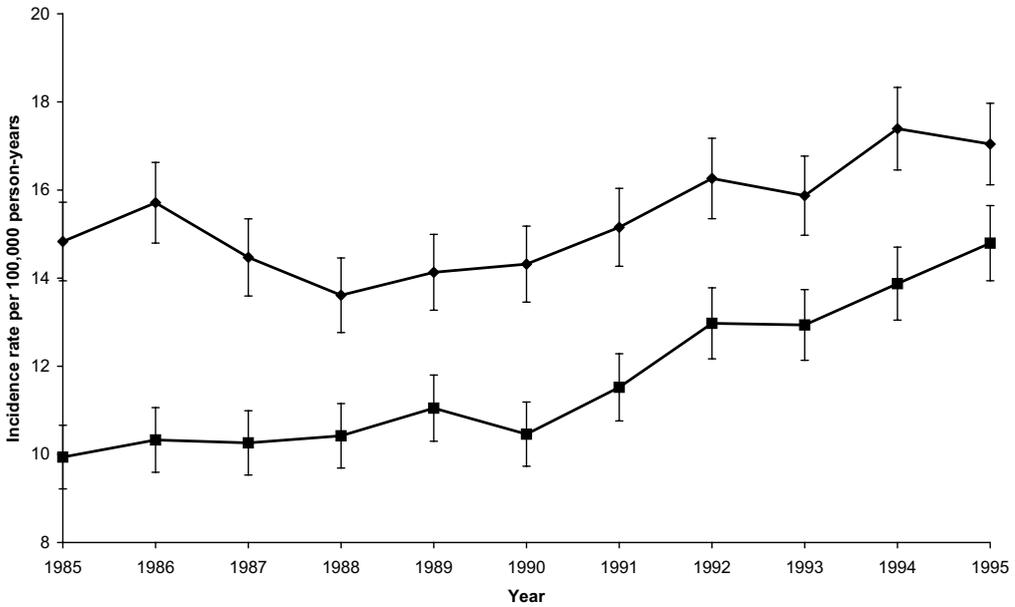
## RESULTS

### Admissions

In the period 1985-1995 we identified a total of 22,266 admissions for acute pancreatitis, in 19,327 (86.8%) of these it concerned a first attack. Of the 9,579 patients admitted with a first attack of acute pancreatitis in the period 1985-1990, 1047 (10.9%) patients experienced a relapse within 5 years and 608 (6.4%) patients developed chronic pancreatitis within 5 years.

Males (54.8%) and people with a sickfund health insurance (70.7% vs. 61.5% in the population) -representing the lower income groups- were overrepresented. The mean age at first admission for acute pancreatitis was 53.8 years (95% CI; 53.5- 54.1) for males and 59.3 years (95% CI; 58.9-59.7) for females.

The average duration of a hospital stay for acute pancreatitis decreased from 25.2 (95% CI; 24.1-26.4) days in 1985 to 20.8 (95% CI; 19.9-21.7) in 1995.



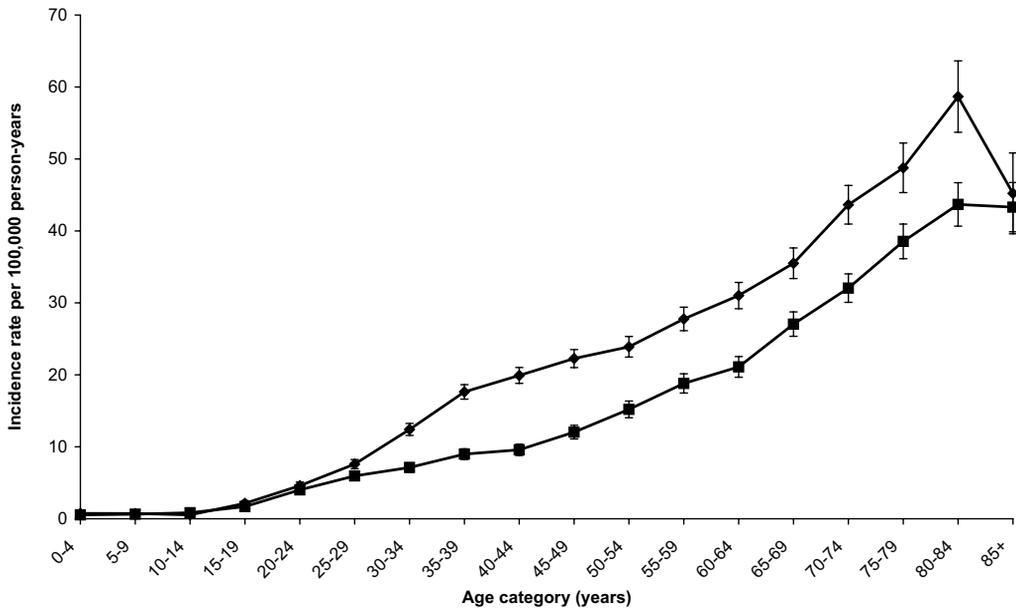
**Figure 1** Annual gender specific incidence rate of acute pancreatitis per 100,000 person-years in the Netherlands between 1985 and 1995 (Bars represent 95% CI). Male (◆), female (■).

## Incidence

The observed incidence rate of acute pancreatitis increased from 12.4/100,000 person-years (95% CI; 11.8-12.9) in 1985 to 15.9/100,000 person-years (95% CI; 15.3-16.5) in 1995. This rise in the observed incidence rate was explained by a rise in the incidence rate of acute pancreatitis as primary discharge diagnosis. The incidence rate of acute pancreatitis as secondary discharge diagnosis remained stable between 1985 and 1995.

Figure 1 shows the gender specific incidence curves, which indicate that the incidence of acute pancreatitis was consistently higher among men than among women and increased in both sexes during the study period. In men, the incidence of acute pancreatitis increased from 14.8/100,000 person-years (95% CI; 13.9-15.7) in 1985 to 17.0/100,000 person-years (95% CI; 16.1-18.0) in 1995. In women the increase was from 9.9/100,000 person-years (95% CI; 9.2-10.7) in 1985 to 14.8/100,000 person-years (95% CI; 13.9-15.6) in 1995. Figure 1 shows that the increase did not occur steadily over the years but appeared predominantly after 1990.

The incidence rate of acute pancreatitis rose markedly with age (figure 2). An increase of the incidence during the period 1985-1995 was seen primarily among the elderly. Recalculation of the annual incidence rates by reference to the age and



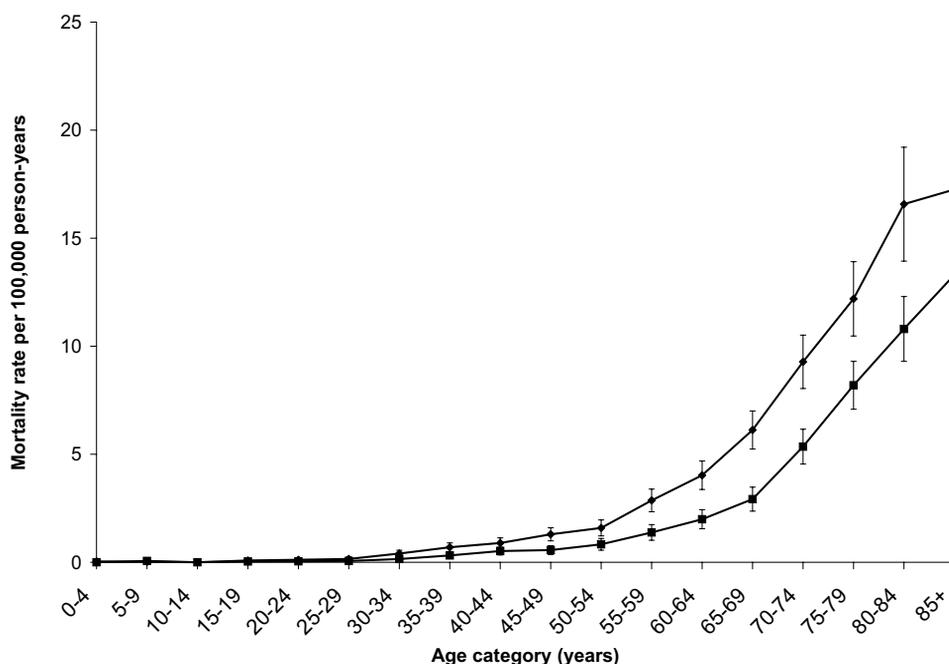
**Figure 2** Age and gender specific incidence rates of acute pancreatitis in the Netherlands in the period 1985-1995 (Bars represent 95% CI). Male (◆), female (■).

gender structure of 1985 showed an increase of 12.4 per 100,000 person-years in 1985 to 14.8 per 100,000 in 1995.

### Mortality rate and case-fatality proportion

The overall annual mortality rates for acute pancreatitis remained fairly stable at 1.5/100,000 person-years between 1985 and 1995. The mortality was very low in children and young adults, but increased rapidly after 30 years of age to 14.4/100,000 person-years (95% CI; 12.7-16.1) in the age category above 85 years (figure 3).

Figure 4 shows that the case-fatality proportion declined from 13.2% (95% CI; 11.1-15.2) to 9.5% (95% CI; 7.9-11.1) in men ( $p=0.005$ ) and from 13.0% (95% CI; 10.6-15.5) to 10.0% (95% CI; 8.3-11.8) in women ( $p=0.043$ ) between 1985 and 1995. The case-fatality of first admissions declined from 14.3% (95% CI; 12.6-16.1) in 1985 to 10.7% (95% CI; 9.4-12.0%) in 1995. The case-fatality of relapses remained stable at approximately 3.2%. Figure 5 illustrates that the case-fatality proportion increases rapidly with age up to 38.2% (95% CI; 32.1-44.3) in men aged 85 years and over and up to 30.7% (95% CI; 27.1-34.4) in women aged 85 years and over.



**Figure 3**  
Age and gender specific mortality rates of acute pancreatitis in the Netherlands in the period 1985-1995 (Bars represent 95% CI). Male (♦), female (■).

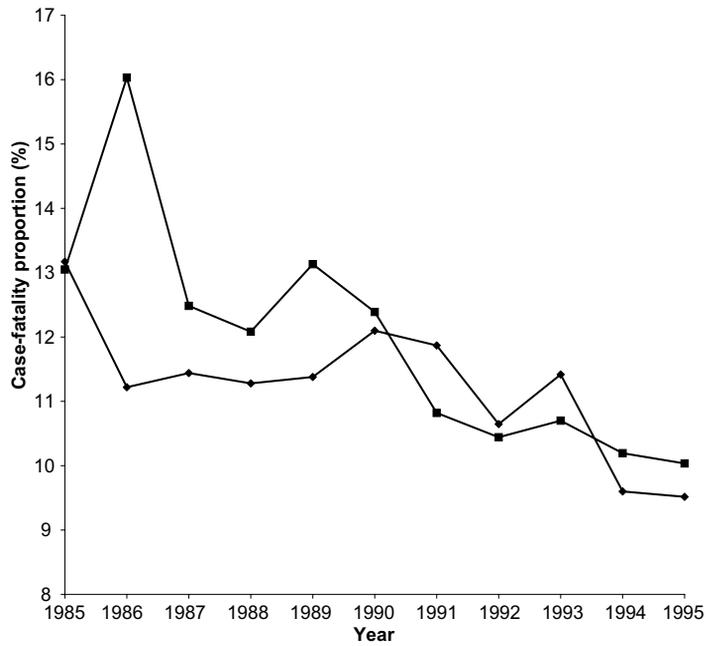
## Etiology

During the study period the total amount of pure alcohol consumed per inhabitant steadily declined from 8,5 liters in 1985 to 8,0 liters in 1995. The incidence of gallstone diseases increased slightly from 143.5/100,000 person-years in 1985 to 159.5/100,000 person-years in 1995 ( $r_s$  with incidence of acute pancreatitis = 0.76,  $p < 0.01$ ). The incidence of endoscopic procedures to the pancreatic and bile ducts increased from 38.2/100,000 person years in 1991 to 61.2 per 100,000 person-years in 1995 ( $r_s$  with incidence of acute pancreatitis = 0.90,  $p < 0.05$ )

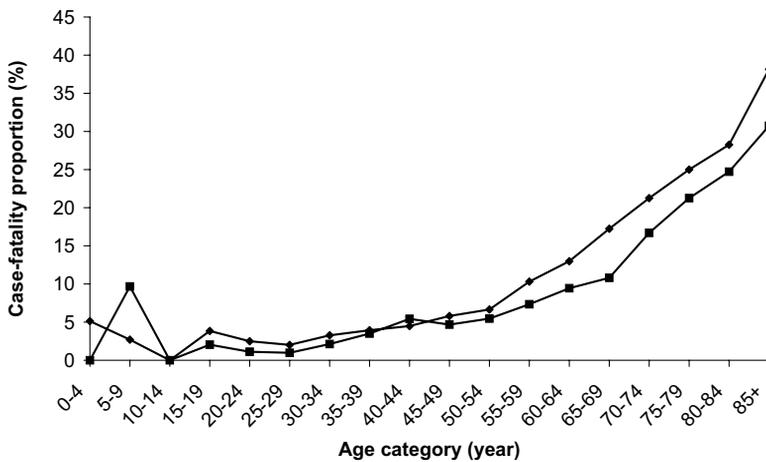
## Validation of NISHC

Of the 17 consecutively enrolled patients in a prospective study on acute pancreatitis, 13 (76%) were correctly notified to Prismant.

We retrieved the medical records of 101 patients from the University Hospital Rotterdam, who were notified to Prismant with a discharge diagnosis code for acute pancreatitis in 1985, 1990 and 1995 by the University Hospital Rotterdam. Eighty-three (82.2%) were correctly coded with a discharge code for acute pancreatitis. This



**Figure 4**  
Annual gender specific case-fatality proportion of acute pancreatitis in the Netherlands in the period 1985-1995. Male (♦), female (■).



**Figure 5**  
Age and gender specific case-fatality proportion of acute pancreatitis in the Netherlands in the period 1985-1995. Male (♦), female (■).

percentage was consistent over the years 1980, 1985, and 1995. Of the 18 remaining patients, nine patients had an amylase value less than double the upper normal limit and could therefore not be classified as acute pancreatitis. Furthermore, we found no mention of abdominal pain in the medical records of an unconscious patient admitted to a coronary care unit, four patients had chronic pancreatitis, and four patients were admitted for other diseases.

## DISCUSSION

We performed a nationwide study to assess annual age and gender specific incidence rates of acute pancreatitis in the Netherlands between 1985 and 1995. We observed a rise in the incidence of acute pancreatitis from 12.4/100,00 person-years in 1985 to 15.9/100,000 person-years in 1995 (28.2%). This trend is consistent with the results of several other studies.(1,3,8-11) It has been advocated that the increase in incidence rate found in previous studies may be explained by improved diagnostic procedures. During 1985-1995 however, diagnostic procedures for acute pancreatitis underwent no considerable changes and it is therefore unlikely that changed procedures can explain the observed rise in incidence. Although there is no evidence that hospitalization patterns for acute pancreatitis have changed during the study period, one cannot exclude that certain factors may have influenced the observed incidence rates in this retrospective study.

A study on the incidence of acute pancreatitis conducted in Scotland over the period 1985-1995 showed an increase in the incidence from 25.8/100,000 inhabitants in 1985 to 41.9/100,000 inhabitants in 1995. (15) A previous study in the Netherlands observed a rise in the rate of acute pancreatitis from 5.7/100,000 in 1969 to 8.1/100,000 in 1976 for men and a stable incidence of 7.3/100,000 person years for females.(8) On the assumption that the estimation of the incidence rates were comparable, this would translate in a rise in incidence of acute pancreatitis of 198.2% for men and 102.7% for women from 1969 to 1995.

We found strong associations between age and gender and the incidence of acute pancreatitis. This is consistent with the results of other studies.(3,11) However, the increase in incidence cannot be solely explained by an aging population as the incidence of acute pancreatitis standardized for age and gender also showed a rise. Although the incidence of acute pancreatitis increased between 1985 and 1995, the annual mortality rate remained fairly stable. This is due to a drop in the case-fatality, which may be explained by more efficacious intensive care treatment or by a higher proportion of patients with mild acute pancreatitis. However the case-fatality was still 10% in 1995, which is high compared with the 4.5% which was found in a similar study in Scotland.(15) One of the reasons for this discrepancy may be an underes-

timation of mild acute pancreatitis in our study. The mortality rate and case-fatality proportion rose profoundly with age; in people aged 75 years and over case-fatality was more than 30%. Fan et al. showed that this higher mortality was accounted for by a higher occurrence of deaths related to concomitant diseases.(16) The case-fatality in first attacks was markedly higher than in relapses, which was consistent with other studies.(9, 17-20)

Previous studies have shown that in 12 to 42 % of patients who die of acute pancreatitis, the diagnosis is first discovered at autopsy. (4,21) As not all patients dying in hospital are autopsied, the incidence of acute pancreatitis may have been underestimated. Autopsy data that are available are used for coding of discharge diagnoses. This is exemplified by the fact that of 84 patients who had a fatal attack of acute pancreatitis and were identified in the database to originate from the University Hospital Rotterdam, 45 were first discovered at autopsy.

About 6% of patients who presented with a first attack of acute pancreatitis developed a chronic pancreatitis within a period of 5 years. This figure is considerably lower than the 24% found in a study by Reid.(17) These differences are probably explained by differences in duration of follow-up.

During the study period the total amount of pure alcohol consumed per inhabitant steadily declined from 8,5 liters in 1985 to 8,0 liters in 1995. Although causal inferences cannot be drawn from ecological data it seems unlikely that the overall increase in incidence of acute pancreatitis during the study period can be explained by an overall decrease in alcohol consumption. On the other hand the incidence rates of gallstone diseases and the incidence of endoscopic procedures to the pancreatic and bile ducts were positively correlated with the incidence of acute pancreatitis. The incidence rate of gallstone diseases increased primarily after 1991, as did the incidence rate of acute pancreatitis. Unfortunately we had no data on the number of endoscopic procedures performed in the period 1985-1990, but the numbers are likely to have increased more in the period 1991-1995 than in the preceding period. Estrogen use is likely to have increased in the studied period and may partly explain the rise in incidence of acute pancreatitis in women.

The NISHC contains information on at least 99 % of all admissions to general- and academic hospitals in the Netherlands. Hospitals supply data to Prismant on a monthly basis. Thorough validation of the data with feedback to the hospitals increases accuracy of the data.

It has been suggested that hospital disease registry systems are an unreliable source for incidence calculations. (5) Our limited validation procedures showed that 83% of acute pancreatitis admissions notified to Prismant by the University Hospital Rotterdam in the years 1985, 1990 and 1995 were correctly coded, which could mean that the incidence rates in this study are overestimated by 10-20%.

On the other hand, we found that 76% of patients identified as having acute pan-

creatitis in a prospective study were notified to Prismant. Due to the underreporting on the one hand, and the overreporting due to miscoding, the observed incidence rates may reflect the true rates. Since these errors are not likely to have changed considerably during the study period, we do not think they can explain the observed trend.

In conclusion, we observed an increase in the incidence of acute pancreatitis by 28% in the Netherlands between 1985 and 1995. With a trend downward in case-fatality, the mortality remained stable in this period.

## ACKNOWLEDGEMENTS

The financial support provided by the Netherlands Organization for Scientific Research (NWO) ZonMW, and the financial support of the foundation 'Vereniging Trustfonds Erasmus Universiteit Rotterdam' is gratefully acknowledged. The authors thank R.R.M. de Groot from Prismant Health Care Information for her contribution in collection of the data.

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## Incidence of acute pancreatitis in the general population

2.2

## **Incidence of acute pancreatitis in the general population**

***Introduction:** Incidence studies on acute pancreatitis have largely been based on hospital discharge data. We estimated the incidence and referral rate of a first attack of acute pancreatitis in the general population.*

***Methods:** We conducted a population-based cohort study in the Integrated Primary Care Information (IPCI) general practitioners database in the Netherlands. We identified all patients with a diagnosis of acute pancreatitis (ICPC: D99.4, free text) and all patients with an elevated amylase or lipase between 1 January 1995 and 1 May 1999. For all potential cases additional clinical information was obtained to validate the diagnosis.*

***Results:** The total study population comprised 242,451 patients, who contributed a total of 599,368 person-years. 110 patients had a computerised primary care history compatible with a first episode of acute pancreatitis. Acute pancreatitis could be substantiated in 84 (76%). Biliary pancreatitis was more frequent in women (46% vs. 35%), alcohol-related pancreatitis was more frequent in men (29% vs. 3%). The overall incidence rate of a first attack of acute pancreatitis standardised for the age and gender structure of the Dutch population in 1995 was 14.2/100,000 person-years. The incidence of acute pancreatitis was higher in men than in women and rose markedly with age. 82 out of 84 patients with acute pancreatitis were referred to hospital.*

***Conclusion:** Hospital-based incidence studies on acute pancreatitis are comparable to incidence studies based on general population data.*

## INTRODUCTION

Acute pancreatitis is an inflammatory disease of the pancreas with considerable morbidity and mortality. Clinically, acute pancreatitis is characterised by severe acute abdominal pain, nausea, and vomiting. Laboratory examinations usually reveal elevated levels of serum amylase and lipase. Gallstones and alcohol are the most important risk factors for acute pancreatitis. Other risk factors include hyperlipidemia, hypercalcemia, ERCP and trauma. In 10 to 25% of the patients with acute pancreatitis, no obvious risk factors are present.(1)

The incidence of acute pancreatitis varies around 10 to 40 per 100,000 inhabitants.(2-7) Recent studies have shown an increase in the incidence of acute pancreatitis.(3,8) Incidence studies on acute pancreatitis have been based on hospitalisation data. These studies may underestimate the true incidence rate of acute pancreatitis if not all patients with acute pancreatitis are referred to hospital. We conducted a study within a general practitioners database to estimate the incidence and referral rate of a first episode of acute pancreatitis in the general population.

## METHODS

### Setting

In the Dutch health care system, nearly every citizen is enrolled in the practice of a general practitioner (GP). The GP acts as a gatekeeper in the health care system and co-ordinates the secondary medical care for patients registered in the GP practice.(9) In the Netherlands, over 400,000 patients are registered with one of the 150 GPs who participate in the Integrated Primary Care Information (IPCI) database project. Medical data are continuously recorded and sent anonymously to the department of Medical Informatics of the Erasmus Medical Center Rotterdam in order to be used for research projects. The computerised information contains demographic data, GP notes, diagnoses and findings, laboratory values and prescriptions. Summaries of the hospital discharge letters or information from specialists are included as free text. Patient complaints and diagnoses are coded according to the International Classification for Primary Care (ICPC). Prescription drugs are coded according to the Anatomical Therapeutic Chemical classification (ATC). To maximise completeness of the information, GPs participating in the IPCI project are not allowed to have a system of paper records besides the electronic medical records. The IPCI database has shown to be a valid database for the conduct of epidemiological research.(10)

## **Study population**

Our study population comprised all patients who were permanently registered with one of the participating GP practices. Patients were followed from January 1st 1995, the date of first participation of the GP in IPCI, or the date of patient registration in the GP practice, whichever was latest. Follow-up ended upon death, transferring out of the GP practice, the occurrence of a first episode of acute pancreatitis or chronic pancreatitis or May 1st 1999, whichever came first. We excluded all patients with a history of pancreatitis before the inclusion date.

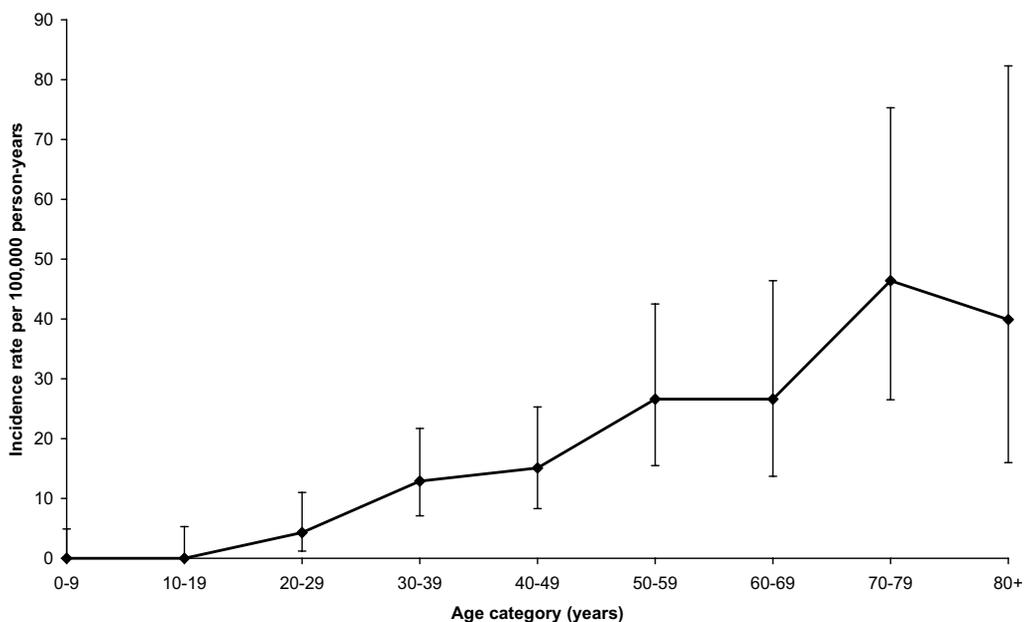
## **Case ascertainment and definition**

By means of a computerised algorithm we identified all patients with an ICPC-code for pancreatitis (D99.4), and all patients with an elevated serum amylase, serum lipase or urinary amylase. To avoid potential underascertainment of acute pancreatitis due to non-coded information (for example from discharge letters) we included a free text search on pancreas and pancreatitis.

The computerised medical records were reviewed manually for all potential cases and additional information (discharge letters and laboratory examinations) was requested from the GP if acute pancreatitis was suspected. All cases were classified as either definite, probable, chronic, or excluded. Acute pancreatitis was labelled definite when there was a clinical picture compatible with acute pancreatitis combined either with an increase in serum amylase or lipase of more than two times the upper limit of normal, or with confirmatory evidence of acute pancreatitis at imaging procedures, laparotomy or autopsy. Acute pancreatitis was labelled probable if the medical record explicitly mentioned that the patient experienced an episode of acute pancreatitis, but no further information was available. Chronic pancreatitis was defined by the presence of exocrine pancreatic insufficiency, pancreatic calcifications, or irregular pancreatic ducts.

## **Analyses**

Age and gender specific incidence rates of acute pancreatitis were calculated by dividing the number of patients with a first episode of acute pancreatitis by the amount of person time in the study population. Ninety-five percent confidence intervals (95% CI) were calculated on the basis of a Poisson distribution. Overall incidence rates were standardised to the age and gender structure of the Dutch population in 1995.



**Figure 1**  
Age specific incidence rates of a first attack of acute pancreatitis.

## RESULTS

The total study population comprised 242,451 patients, who contributed a total of 599,368 person-years of experience to the study. Ninety-one patients were excluded as they had a history of acute pancreatitis before entry into the study. We identified 110 patients who had a computerised history compatible with a first episode of acute pancreatitis and for whom additional information was requested from the GP. After review of this information, the diagnosis could not be substantiated in 26 patients (24%), in 26 (24%) patients the diagnosis was probable, and 58 (53%) patients had a definite diagnosis of acute pancreatitis. Of the 84 patients with definite or probable acute pancreatitis, 49 (58%) were male and the average age of the cases was 55.5 (SD 17.1) years. Twenty-one (25%) patients had no obvious cause for their acute pancreatitis episode. In the others, acute pancreatitis was probably related to gallstones (n=33), alcohol abuse (n=17), ERCP (n=7), pancreas malignancy (n=4), HIV disease (n=1), and hypertriglyceridemia (n=1). Biliary pancreatitis was more frequent in women (46% vs. 35%), alcohol-related pancreatitis was more frequent in men (29% vs. 3%). Five patients (6%) died during their first attack of acute pancreatitis. Two (2%) patients with definite pancreatitis were not referred to hospital. Both had acute abdominal pain

and a serum amylase or lipase of more than five times the upper limit of normal. The course was uneventful in both patients. The overall incidence rate of a first episode of acute pancreatitis was 14.0/100,000 person-years (95% CI: 11.0-17.0). The incidence rate standardised for the age and gender structure of the Dutch population in 1995 was 14.2/100,000 person-years. The incidence of acute pancreatitis was higher in men than in women and rose markedly with age (Figure 1).

## DISCUSSION

We conducted a study into the incidence of a first episode of acute pancreatitis in the general population. The overall incidence rate standardised for the age and gender structure of the Dutch population in 1995 was 14.2/100,000 person-years. The incidence of acute pancreatitis was markedly higher in men and in the elderly. Ninety-eight percent of all patients with a first episode of acute pancreatitis was referred or admitted to hospital.

Previous studies reporting the incidence of acute pancreatitis were based on hospitalisation data. (2-7,11,12) As we studied the incidence of acute pancreatitis in the general population, we had the opportunity to assess the true incidence rate and the potential underestimation due to non-referral in previous studies. Out of 84 patients with acute pancreatitis, only 2 had not been referred to hospital. As almost all patients were referred, underestimation of the incidence of acute pancreatitis due to non-referral of patients will be limited in hospital-based studies.

A study on the incidence of acute pancreatitis in the Netherlands based on hospital discharge diagnoses showed an overall incidence of 15.9/100,000 person-years in 1995.(8) This study concerned both first admissions and relapses of acute pancreatitis. The incidence of first admissions in this study (13.7/100,000 person-years; unpublished data) is similar to the incidence of a first attack of acute pancreatitis in our present study. If one only considers the number of patients that were referred to hospital, the incidence rate in our present study would be 13.9/100,000 person-years. The number of studies that reported the incidence of first attacks of acute pancreatitis is limited. (2,6,11,12) Two studies in Malmö (S) and North-East Scotland showed incidence rates of 23-24/100,000 person-years, two other studies in Nottingham and Bristol (UK) showed incidences of 9-11/100,000 person-years.

Inherent to an incidence study based on computerised medical records is the fact that we may have underestimated the incidence of acute pancreatitis due to undiagnosed acute pancreatitis. In a substantial number of patients with fatal acute pancreatitis, the diagnosis is first discovered at autopsy.(13) As the number of performed autopsies is low, diagnoses of acute pancreatitis may be missed. In addition, not all patients with acute pancreatitis may seek medical attention. To limit underascertain-

ment we used broad search criteria and a free text search on pancreas and pancreatitis. We limited misdiagnosis of acute pancreatitis by checking the computerised medical files and by requesting additional information from the GP if acute pancreatitis was suspected.

## CONCLUSION

The overall incidence of a first attack of acute pancreatitis in the general population is 14.2/100,000 person-years. Ninety-eight percent of all patients with acute pancreatitis were referred to hospital. Underestimation due to non-referral is therefore limited in hospital-based incidence studies on acute pancreatitis.

## ACKNOWLEDGEMENTS

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CHAPTER 3

*three*

*Drug-induced  
acute pancreatitis:  
descriptive studies*



Drug-associated acute pancreatitis:  
21 years of spontaneous reporting  
in the Netherlands

3.1

## **Drug-associated acute pancreatitis: 21 years of spontaneous reporting in the Netherlands**

*Introduction:* Drugs are considered a rare cause of acute pancreatitis. We conducted a descriptive study to assess which drugs have been associated with acute pancreatitis in spontaneous adverse drug reaction reports in the Netherlands.

*Methods:* Our study is based on reports of drug-associated acute pancreatitis which were notified to the Netherlands Center for Monitoring of Adverse Reactions to Drugs and the Netherlands Pharmacovigilance Foundation LAREB between January 1st 1977 and January 1st 1998. We used an algorithm to validate the diagnosis and to assess the causal relationship between acute pancreatitis and use of the suspected drug.

*Results:* A total of 55 cases were available for review. We excluded 11 (20.0%) reports, as we could not confirm the diagnosis of acute pancreatitis. Another 10 (18%) cases were excluded since the causal relationship with the suspected drug was unlikely.

In the remaining 34 reports, acute pancreatitis was labeled as definite in 11 (32%) and as probable in 23 (68%). 24 (71%) patients were female. The age of the patients ranged from 17 to 84 years with a median of 41. Of these 34 cases, 27 (79%) recovered, 5 (15%) died and in 2 (6%) the outcome was unknown. Azathioprine, cimetidine, interferon- $\alpha$ , methyl dopa, metronidazole, olsalazine, and oxyphenbutazon all had a definite causal relationship with acute pancreatitis. Doxycycline, enalapril, famotidine, ibuprofen, maprotiline, mesalazine and sulindac had a probable causal relationship with acute pancreatitis.

*Discussion:* A variety of drugs was associated with acute pancreatitis in Dutch adverse drug reaction reports. Quantitative information about drug-induced pancreatitis is scanty. Epidemiological studies to assess the risk of drug-induced acute pancreatitis are therefore needed.

## INTRODUCTION

Acute pancreatitis is a severe disease with considerable morbidity and mortality. The incidence of acute pancreatitis seems to be rising in Western countries.(1-5) Despite advanced critical care, the case-fatality proportion remains around 5-10%.(1,3,6,7) Gallstones and alcohol are the most important risk factors for acute pancreatitis.(8-10) Other risk factors include hyperlipidemia, hypercalcemia, ERCP and trauma. In 10 to 25% of the patients with acute pancreatitis, no obvious risk factors are present.

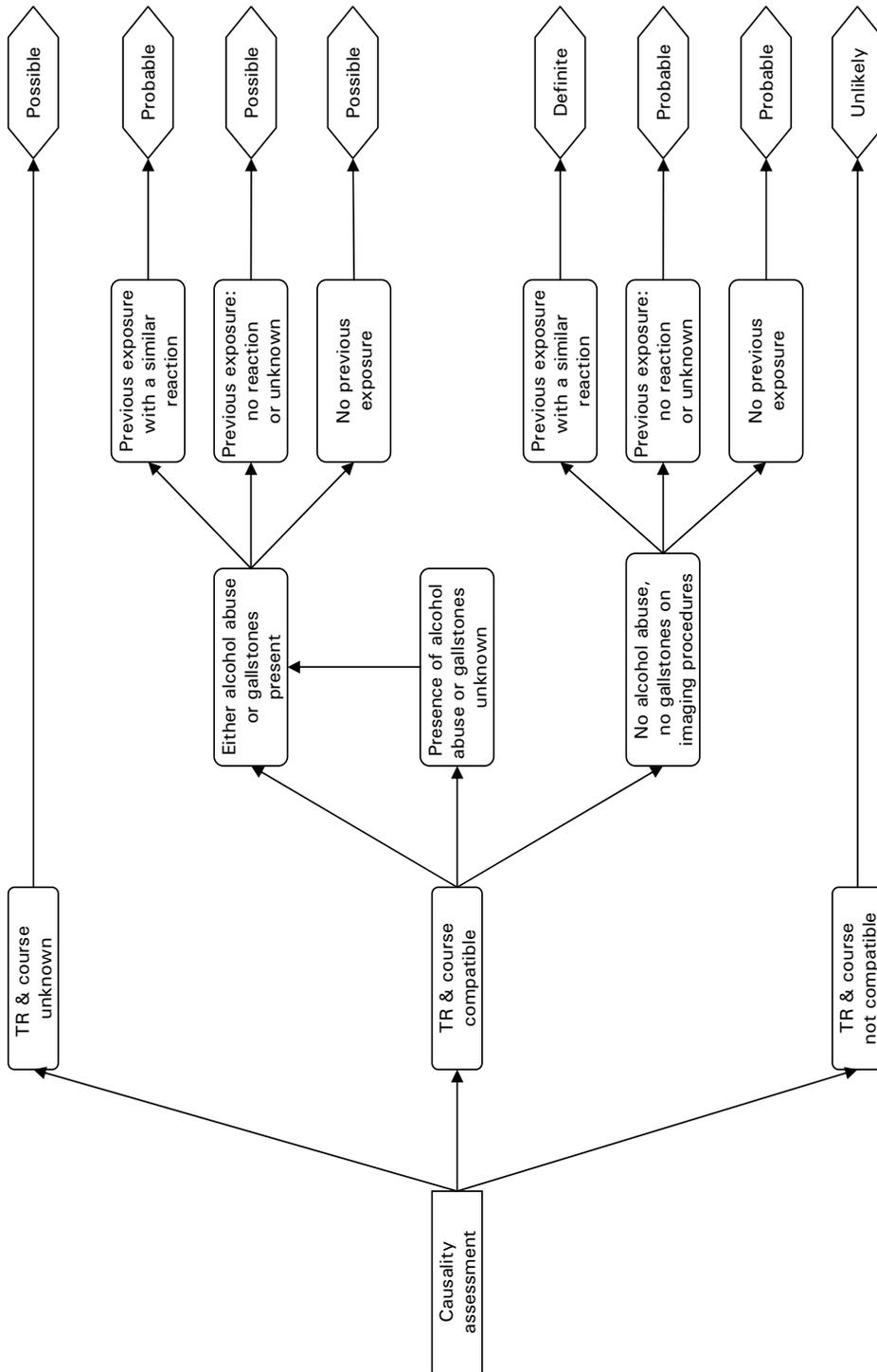
Drugs are rarely associated with the occurrence of acute pancreatitis.(11-14) The pathogenesis of drug-induced acute pancreatitis has not been clarified yet.

The spontaneous adverse reaction-reporting scheme has operated since the early sixties in the Netherlands. From 1977 until 1998, the Netherlands Center for Monitoring of Adverse Reactions to Drugs of the Inspectorate for Health Care and the Netherlands Pharmacovigilance Foundation LAREB received 55 spontaneous reports of potential drug-induced acute pancreatitis. We conducted a descriptive study to assess which drugs were associated with acute pancreatitis in Dutch adverse drug reaction (ADR) reports.

## METHODS

All reports of drug-associated acute pancreatitis which had been reported to the Netherlands Center for Monitoring of Adverse Reactions to Drugs and the Netherlands Pharmacovigilance Foundation LAREB between January 1st 1977 and January 1st 1998 were independently reviewed by two of the authors (IA, EP), as to the probability of the diagnosis of acute pancreatitis, and as to the likelihood of a causal relationship with the suspected drug. Discrepancies were discussed in a consensus meeting (IA, EP, BHCh). Agreement was reached on all reports.

The diagnosis acute pancreatitis was labeled as definite when acute pancreatitis was confirmed by computer tomography (CT), laparotomy or autopsy. The diagnosis was also considered definite when positive findings on ultrasound were combined with abdominal pain and an elevated level of serum amylase or lipase. Acute pancreatitis was labeled as probable when two out of the following three criteria were present: positive findings on ultrasound examination, abdominal pain, elevated serum amylase or lipase. We defined a swollen or enlarged pancreas, an unsharp or vague bordered pancreas, peripancreatic fat infiltration, and necrosis of the pancreas on CT or ultrasound examination as positive signs of acute pancreatitis. Cases were excluded if above-mentioned criteria were not met, or if signs of chronic pancreatitis were found at endoscopic retrograde cholangiopancreatography (ERCP), surgery or autopsy. We defined pancreatic calcifications, or an irregular pancreatic duct as signs



**Figure 1**  
 Drug-associated acute pancreatitis: assessment of a causal relationship with the suspected drug in absence of rechallenge data.  
 TR = time relationship between first intake of the drug and onset of acute pancreatitis.

of chronic pancreatitis.

The causal relationship between acute pancreatitis and the suspected drug was assessed according to figure 1 if no data on rechallenge were provided. The causal relationship was classified *possible* when other risk factors for acute pancreatitis were present, or when the presence of gallstones or alcohol abuse (>5E/24h) was not known. In patients with a relapse of acute pancreatitis after rechallenge the causal relationship was considered *definite*.

## RESULTS

From 1977 until 1998 the Netherlands Center for Monitoring of Adverse Reactions to Drugs received 45 reports and the Lareb Netherlands Pharmacovigilance Foundation received 13 reports of drug-associated acute pancreatitis. Three of the 58 reports were notified to both reporting centers, leaving 55 episodes of suspected drug-induced acute pancreatitis.

Eleven (20%) reports were excluded, as we could not confirm the diagnosis of acute pancreatitis. In 6 cases the criteria for definite or probable acute pancreatitis were not met, and 5 cases concerned chronic pancreatitis. In ten (18%) cases the causal relationship between the suspected drug and the occurrence of acute pancreatitis was labeled unlikely because of an incompatible time relationship between start of drug treatment and development of acute pancreatitis or because of a relapse after discontinuation of the drug. These cases were excluded from the analysis.

In the remaining 34 case-histories, the diagnosis of acute pancreatitis was considered definite in 11(32%) and probable in 23(68%) cases. A discharge summary could be obtained for 33 of these 34 (97%) adverse drug reaction reports. The remaining report had enough clinical data for a reliable assessment. It concerned 24 (71%) females and 10 (29%) males. The age ranged from 17 to 84 years with a median of 41. Twenty-seven cases (79%) were admitted with abdominal pain, three (9%) were admitted with back pain and in four (12%) the symptoms on admission were unknown. Thirty-two cases (94%) had an elevated level of serum amylase or lipase, 1 case (3%) had a normal level of serum amylase and in 1 case (3%) no enzyme levels were mentioned. CT scanning and US examination revealed signs of acute pancreatitis in 7 and 9 cases respectively.

The causal relationship with the suspected drug was considered *definite* in 9 (26%), *probable* in ten (29%), and *possible* in 15 cases (44%). Table 1 lists patient characteristics, other risk factors for acute pancreatitis, the time- and causal relationship between drug intake and development of symptoms and the outcome in our 34 patients.

**Table 1**  
**Characteristics of 34 reports of drug-associated acute pancreatitis**

G	Age	Drug	Dosage(*)	TR	Gallst.	alc. abuse	CR	Outc.	Remarks
V	33	alendronate	10 mg	21 days	yes	?	possible	†	-
V	42	azathioprine	50 mg	10 days	no	?	definite	rec.	rechallenge +
V	58	azathioprine	75 mg	19 days	no	?	definite	rec.	rechallenge +
V	39	azathioprine	50 mg	25 days	no	no	probable	rec.	-
V	27	azathioprine	100 mg	15 days	?	?	possible	rec.	-
V	57	captopril	50 mg	2 years	no	no	possible	rec.	treatment was continued, another attack after 18 months
M	67	ciclosporine/ isradipine	?	59 days	no	no	possible	†	acute pancreatitis after kidney transplantation
M	38	cimetidine	800 mg	5 days	no	no	definite	rec.	developed acute pancreatitis after cimetidine 9 years ago
V	67	ciprofibrate	100mg	23 days	?	no	possible	†	ciprofibrate for hyperlipidemia
M	59	didanosine	400 mg	95 days	no	?	possible	†	HIV +
M	23	doxycycline	100 mg	1 day	no	no	probable	rec.	-
M	60	enalapril	5 mg	96 days	no	no	probable	rec.	inadequate rechallenge
M	62	famotidine	20 mg	some months	no	no	probable	†	-
V	25	ibuprofen	3600 mg	10 days	no	no	probable	rec.	up to 8 tablets (600 mg) a day
M	40	interferon- $\alpha$	3 MU TIW	15 weeks	no	5U/day	definite	rec.	rechallenge +
V	59	jotrolan	?	6 hours	?	?	possible	?	contrast agent used at ERCP, 800 mg of gentamycine was added to the contrast agent
V	84	jotrolan	?	4 hours	yes	?	possible	?	contrast agent used at ERCP, 800 mg of gentamycine was added to the contrast agent
V	27	lamivudine	300 mg	206 days	no	?	possible	rec.	HIV +
V	46	maprotiline	75 mg	10 days	no	no	probable	rec.	-
V	26	mesalazine†	3000 mg	16 days	no	no	probable	rec.	azathioprine-induced acute pancreatitis 4 months later
M	36	mesalazine†	1500 mg	7 days	no	no	probable	rec.	-
V	31	mesalazine†	3000 mg	28 days	no	no	probable	rec.	-
V	23	mesalazine	1500 mg	8 days	?	no	possible	rec.	-
V	61	methyl dopa†	?	14 days	no	?	definite	rec.	rechallenge +
V	69	methyl dopa†	500 mg	14 days	yes	?	definite	rec.	rechallenge +

V	73	metronidazole/ tetracycline/ bismuth	1500 mg 2000 mg 480 mg	1 day	no	?	possible	rec.	history of carcinoma ampulla Vateri
V	46	metronidazole‡	2000 mg	1 day	no	no	definite	rec.	4 and 7 years ago acute pancreatitis after metronidazole
M	34	nelfinavir/ nevirapine/ AZT	1000 mg 200 mg 200 mg	22 days	no	?	possible	rec.	HIV +, CMV +, cryptosporidium +
V	23	olsalazine‡	1500 mg	5 days	no	no	definite	rec.	rechallenge +
V	32	oxyphenbutaz.‡	200 mg	21 days	no	no	definite	rec.	rechallenge +
V	27	propyfenazon/ paracetamol/ caffeinum	?	?	no	?	possible	rec.	had an attack of acute pancreatitis 4 months earlier
M	57	sulindac	800 mg	1 month	no	no	probable	rec.	3 attacks of acute pancreatitis during 15 months of treatment
V	66	sulindac/ ergotamine	?	?	no	no	possible	rec.	-
V	17	tetracycline	750 mg	8 days	no	?	possible	rec.	mumps virus +

G = gender, TR = time relationship between first intake of the drug and onset of acute pancreatitis, gallst = gallstones, alc. abuse = alcohol abuse, CR = causal relationship between the suspected drug and acute pancreatitis, outc = outcome, ? = unknown, rec. = recovered, = died, (\*) per day, ‡ have been reported in case-reports.

## DISCUSSION

In this case series, we evaluated 55 Dutch reports of drug-associated acute pancreatitis which resulted in 14 drugs with a probable or definite association with the outcome: azathioprine, cimetidine, doxycycline, enalapril, famotidine, ibuprofen, interferon- $\alpha$ , maprotiline, mesalazine, methyldopa, metronidazole, olsalazine, oxyphenbutazon and sulindac. To our knowledge maprotiline and famotidine have not been reported to be associated with acute pancreatitis before.

Most of the 'evidence' of associations between drugs and acute pancreatitis is based on anecdotal case-reports. Reviews mention aminosalicylates, L-asparaginase, estrogens, thiazide diuretics, valproate, azathioprine, corticosteroids, furosemide, mercaptopurine, tetracycline, sulindac, and pentamidine most frequently.(11-14) The WHO has received a total of 2749 reports of drug-associated acute pancreatitis in the period between 1968 and 1993. ACE-inhibitors (n=209), valproate (n=219), H2-receptor-blockers (n=127), sulindac (n=121), azathioprine (n=73), gemfibrozil (n=72), lovastatin (n=72), pentamidine (n=62), and didanosine (n=61) were the most frequently reported drugs.(15)

Despite this relatively large volume of case-based evidence, surprisingly little is known about the epidemiology (incidence and relative risks) and mechanisms of drug-associated pancreatitis. Epidemiological evidence is limited to 2 small case-control studies which have shown an increased risk of acute pancreatitis associated with use of diuretics.(16, 17)

It is well known that the incidence of an adverse effect cannot be validly estimated from spontaneous reports. This is due to large underreporting to voluntary reporting schemes, and the scantiness of information on spontaneous reports which complicates validation of the outcome, and assessment of causality to the suspected drugs. In order to facilitate validation and causality assessment in our case series, we collected additional clinical information. Causality assessment was based on the temporal relationship, effect of dechallenge, rechallenge and the presence of other established causes (e.g. gallstones, excessive alcohol intake, ERCP). Although our assessments were based on retrospective review of discharge summaries that may lack information on the presence of risk factors we excluded 11 out of 55 cases on the basis of a non-ascertained diagnosis, and another 10 were excluded because a causal relationship was unlikely. This shows that thorough evaluation of spontaneous reports is indeed necessary prior to making inferences on any kind of frequency or association.

The mechanism of drug-induced pancreatitis is largely unknown. In general, characteristics of the adverse event such as the temporal relationship, dose response, dechallenge and rechallenge may help in suggesting potential mechanisms. For instance, mesalazine may possibly provoke immunological damage to the pancreas, as rechallenge with small doses can induce relapses of acute pancreatitis within

hours.(18-32) However, one should be careful associating these drugs to acute pancreatitis since inflammatory bowel disease itself may also cause pancreatitis.(33-37) The same argument holds for azathioprine. This drug has often been associated with pancreatitis, even with positive rechallenge, (38-43) but other studies could not confirm this association (44-46).

Localized angioedema with obstruction of the pancreatic duct may be the mechanism by which ACE-inhibitors cause acute pancreatitis.(47) Time intervals between the start of ACE-inhibitor treatment and the onset of acute pancreatitis vary between one day and two years.(47-55) These intervals are consistent with induction times described for ACE-inhibitor induced angioedema.(56-58)

Protopathic bias (prescription of a drug for pro-dromal symptoms of the outcome) may explain the reports regarding use of H2-blockers and acute pancreatitis.(59-61) An argument in favor of a real association is the positive rechallenge that we and others have observed following the re-administration of cimetidine.(60) If true, the mechanism remains unknown but the rapid relapse within 24 hours after re-exposure suggests an idiosyncratic reaction. As compared to cimetidine, famotidine is a relatively new H2 blocker, which may explain why we are the first to report an association between this drug and acute pancreatitis. However, the previous considerations regarding a potential protopathic bias are equally valid for this H2 blocking agent.

Reports of NSAID-induced acute pancreatitis are sparse, and so are hypotheses on a possible biologic mechanism.(62-68) Sulindac seems to stand out, followed by oxyphenbutazon.(69-82) One report has been published on a patient who developed a possible acute pancreatitis as part of a generalized hypersensitivity syndrome to ibuprofen.(83) However, this patient also had parotitis which may explain the hyperamylasemia and systemic lupus erythematosus which in itself may be a risk factor for acute pancreatitis.(8) As for the H2 blockers, the association between NSAID use and acute pancreatitis may be explained by protopathic bias, since analgesics may be used for abdominal pain.

One case has been described previously of a 9-year old girl who developed acute pancreatitis after 14 months of treatment with interferon- $\alpha$  for chronic myelogenous leukemia.(84) In our case series, we described one patient with a recurrence of acute pancreatitis after re-administration of interferon- $\alpha$ , which makes a causal association likely.

Our two reports of methyldopa-associated pancreatitis are consistent with one case which has been published previously.(85) All three cases experienced a positive reaction to rechallenge within hours after intake, which suggests an idiosyncratic reaction (85-87).

The association between metronidazole and acute pancreatitis remains unclear. No mechanism is known but 5 reports have suggested a possible association, (88-92) but a cohort study among 6485 users of metronidazole did not yield one hospitalization

for acute pancreatitis.(93)

In conclusion, a wide variety of different drugs were associated with acute pancreatitis in our Dutch case series. Most of the drugs have been associated before, however, acute pancreatitis due to famotidine and maprotiline has not been reported before. Despite the presence of numerous case-reports on drug-induced acute pancreatitis, quantitative information on this subject is scanty. Large scale epidemiological studies are necessary to assess the risk of drug-induced acute pancreatitis.

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Acute pancreatitis attributed to  
interferon- $\alpha$

3.2

### **Acute pancreatitis attributed to the use of interferon- $\alpha$ -2B**

*Two patients experienced an episode of acute pancreatitis shortly after starting treatment with interferon- $\alpha$ -2B (IFN- $\alpha$ ) for chronic hepatitis C infection. The first patient was a 40-year-old man who developed acute pancreatitis after 15 weeks of IFN- $\alpha$  three MU s.c. thrice a week and ribavirin 1200 mg. After disappearance of symptoms and normalization of laboratory values, oral intake of solid foods and IFN- $\alpha$  therapy were restarted. Within hours a relapse of acute pancreatitis occurred. A rechallenge with IFN- $\alpha$  four days later was followed by a prompt increase in serum lipase and IFN- $\alpha$  therapy was discontinued. The second patient was a 38-year-old man who developed acute pancreatitis two hours after administration of five MU IFN- $\alpha$  s.c. Ultrasound endoscopy showed sludge in the gallbladder. The patient was rechallenged five weeks later with IFN- $\alpha$  three MU s.c. Although serum amylase and lipase increased after re-administration of IFN- $\alpha$ , treatment was continued. The patient was readmitted two weeks later with severe abdominal pain after which IFN- $\alpha$  was discontinued.*

*Considering the temporal relationship between start of IFN- $\alpha$  treatment and development of acute pancreatitis, the absence of other clear etiological factors for acute pancreatitis, disappearance of symptoms after discontinuation of IFN- $\alpha$  and a positive reaction to rechallenge, IFN- $\alpha$  is the most probable cause for development of acute pancreatitis in these patients.*

## INTRODUCTION

Interferon- $\alpha$  is used primarily for the treatment of viral hepatitis and hematological malignancies.(1,2) Interferon- $\alpha$  is formed in reaction to viral infections in vivo and is produced by recombinant DNA technology for therapeutic purposes. The therapeutic activity of interferon- $\alpha$  is incompletely understood. Apart from its antiviral properties, the immunoregulatory and anti-inflammatory activities of interferon- $\alpha$  are of importance.(3)

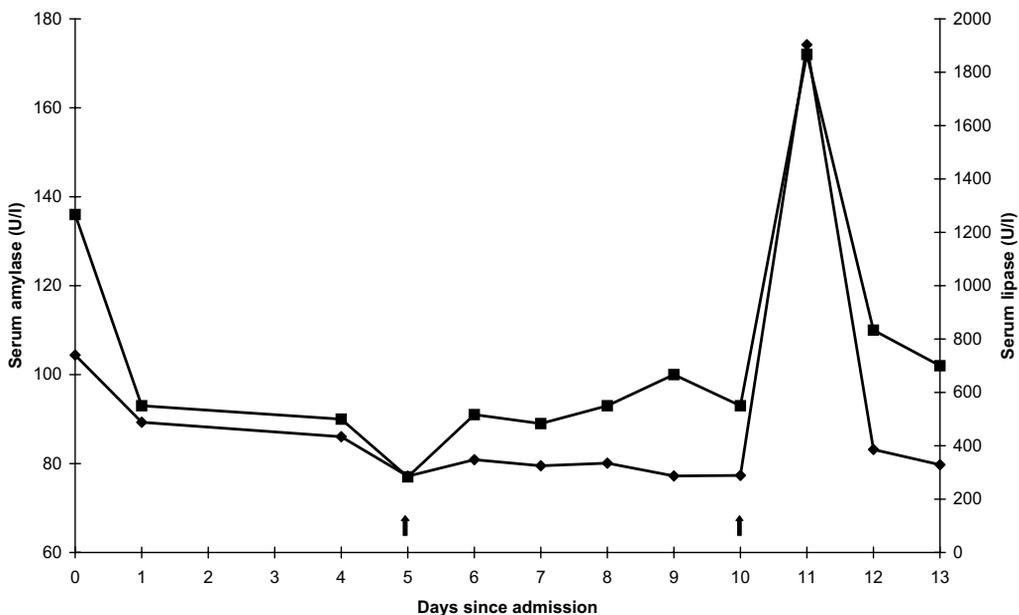
Flu-like adverse reactions are common during interferon- $\alpha$  therapy. These symptoms are generally acute and consist mainly of fever, chills, myalgias and malaise, but anorexia and fatigue may persist.(4) Several serious adverse events have been associated with interferon- $\alpha$ : agranulocytosis, thrombocytopenia, arthritis, thyroid dysfunction, rhabdomyolysis, pneumonitis, retinopathy, and renal insufficiency.(5-12). We describe the case-histories of two patients who developed acute pancreatitis after initiating interferon- $\alpha$ -2B (IFN- $\alpha$ ) therapy for chronic hepatitis C.

## CASE-HISTORIES

### Patient A

A 40-year-old man was admitted with diffuse, progressive abdominal pain that started two days before, as well as nausea, vomiting and diarrhea that had been present for 12 weeks. Non-A-non-B hepatitis had been diagnosed 18 years before admission and the patient had a history of intravenous drug abuse up to nine years before admission. Fifteen weeks before admission, the patient was started on ribavirin 1200 mg daily and IFN- $\alpha$  three MU (s.c.) thrice a week for chronic hepatitis C. The patient used 40 mg omeprazole and 400mg mebeverine daily. The patient used up to five units of alcohol per day. Physical examination revealed diffuse tenderness in the abdomen and rebound tenderness in the right lower abdomen. Laboratory examination showed a gamma-glutamyl transferase of 124 u/l (normal 15-70), a serum amylase of 136 u/l (normal 30-120), a serum lipase of 740 u/l (normal <300) and a C-reactive protein of 30.9 (normal <8.0 mg/l). Calcium, triglycerides, and cholesterol were all within normal limits. Ultrasound examination (US) revealed no gallstones or pancreatic abnormalities.

Five days after admission the complaints had disappeared and amylase and lipase values had returned to normal. As the development of acute pancreatitis was originally attributed to ribavirin, antiviral treatment was restarted with IFN- $\alpha$  alone.



**Figure 1**  
 Serum amylase and lipase of patient A during hospitalization. ■ = serum amylase (normal 30-120),  
 ◆ = serum lipase (normal <300), ↑ = interferon- $\alpha$ -2B, 3 MU.

Within hours after re-administration of IFN- $\alpha$  abdominal pain returned and serum lipase had increased to 348 u/l (figure 1). The restart of solid food in the same period was considered as a possible explanation for the relapse of acute pancreatitis. After attenuation of complaints and normalization of lipase values four days later the patient was therefore rechallenged with IFN- $\alpha$ . Although the patient did not experience clinical symptoms of acute pancreatitis, the serum lipase had increased to 1903 u/l one day later (figure 1). IFN- $\alpha$  was discontinued and the patient remained relapse free during one year of follow-up.

## Patient B

A 38-year-old man was admitted with nausea and severe pain in the left upper abdomen and epigastric area. He had a history of meningitis, multiple episodes of thrombosis of the right subclavian vein necessitating vascular interventions and multiple blood transfusions, post transfusion hepatitis C, and erectile dysfunction. The patient was a teetotaler. Six hours before admission the patient injected papaverine intra-cavernally and two hours before admission he administered his first dose of IFN- $\alpha$  s.c. The patient had used papaverine eight times before without any problems. No other medi-

cation was taken. Physical examination revealed diffuse tenderness most profoundly in the left upper abdomen. Laboratory examinations showed a serum amylase of 137 u/l (normal 0-100), a serum lipase of 1014 u/l (0-190 ), aspartate-aminotransferase 31 u/l (normal 0-30), alanine-aminotransferase 69 u/l (normal 0-30). Serum cholesterol, triglycerides, and calcium levels were all within normal limits. Computerized tomography (CT) and ultrasonography showed no signs of acute pancreatitis, cholelithiasis, or dilated bile ducts. US-endoscopy showed sludge in the gallbladder.

Complaints disappeared and amylase and lipase normalized within 2 days. Five weeks after admission the patient was rechallenged with 3 MU IFN- $\alpha$  s.c. Two-and-a-half hours later serum amylase and lipase had risen to 123 u/l and 456 u/l respectively. However, treatment was continued. The patient presented 2 weeks later with severe abdominal pain in the left upper abdomen and epigastric area. Serum amylase, lipase, cholesterol and triglycerides were within normal limits. CT-scanning, US and endoscopic retrograde cholangiopancreatography (ERCP) showed no signs of gallstones, dilated bile ducts, and no abnormalities of the pancreas. Bile examination showed one single cholesterol crystal. Treatment was not reinitiated and the patient remained without symptoms for the next two years. The patient continued intermittent use of papaverine intra-cavernally without problems.

## DISCUSSION

Considering the temporal relationship between start of IFN- $\alpha$  treatment and development of acute pancreatitis, the absence of other clear etiological factors for acute pancreatitis, disappearance of symptoms after discontinuation of IFN- $\alpha$  and a positive reaction to rechallenge in the 2 case-histories, we conclude that IFN- $\alpha$  is the most probable cause of acute pancreatitis in these patients.

Alcohol abuse, cholelithiasis, ERCP, hypercalcemia and hyperlipidemia are the most common risk factors for acute pancreatitis.(13) Neither of the patients abused alcohol. Although patient A used up to 5 units of alcohol until admission, he was free of alcohol intake during rechallenge. Neither had gallstones, hypercalcemia, or hyperlipidemia and neither patient underwent an ERCP in the weeks preceding the onset of acute pancreatitis. Patient A received IFN- $\alpha$  and ribavirin as anti-viral treatment. An association between ribavirin and acute pancreatitis is unlikely as the patient had a positive reaction to rechallenge to IFN- $\alpha$  after discontinuation of ribavirin. Mebeverine and omeprazole have not been associated with acute pancreatitis. Patient B used papaverine for erectile dysfunction six hours before admission, but had used papaverine injections without problems 8 times before. Moreover, the patient continued use of papaverine for two years after acute pancreatitis without any problems. US-endoscopy showed sludge in the gallbladder of patient B. Although microlithiasis has been associ-

ated with acute pancreatitis,(14) lipase elevation and return of clinical symptoms after reexposure to IFN strongly suggests a causal relation to IFN- $\alpha$ .

Drugs have been recognized as risk factors for acute pancreatitis. (15) Acute pancreatitis attributed to interferon has been described in two patients.(16,17) A 9-year-old girl developed acute pancreatitis after 14 months of treatment with IFN- $\alpha$  for chronic myelogenous leukemia.(16) The other patient concerned a 54-year-old man who received interferon for chronic hepatitis C.(17) Neither of these two patients were rechallenged with interferon. Five patients with HIV treated with didanosine and interferon combination therapy experienced acute pancreatitis. However, didanosine was the most likely causative agent in these patients.(18,19) In a trial of 25 patients treated with fluorodeoxyuridine, leucovorin and IFN for metastatic renal-cell cancer, two patients experienced pancreatitis, mental confusion and volume overload, but the authors concluded that these events were probably cardiogenic in nature.(20) One patient developed two episodes of acute pancreatitis shortly after start with IFN- $\alpha$  for leukemia, but both episodes were preceded by hypercalcemia.(21) Up to January 2000, 105 reports of interferon- $\alpha$ -2b-associated acute pancreatitis have been notified to Schering-Plough (personal communication).

IFN- $\alpha$  has been shown to increase triglyceride levels,(22,23) but this phenomenon cannot explain the occurrence of acute pancreatitis in the above described patients as both patients had normal levels of triglycerides on admission. The mechanism of IFN- $\alpha$ -induced acute pancreatitis remains unknown, but IFN- $\alpha$  should be regarded as a potential cause of acute pancreatitis.

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Drug-induced acute pancreatitis:  
a systematic review

3.3

## **Drug-induced acute pancreatitis: a systematic review**

***Introduction:** Drugs are considered a rare cause of acute pancreatitis. We reviewed the medical literature to summarise the current knowledge on drug-induced acute pancreatitis.*

***Methods:** We conducted a search on drug-induced acute pancreatitis and its associated terms in PubMed (including MEDLINE) during the period 1966-2001. All English, German, French, and Dutch papers on drug-induced acute pancreatitis were retrieved. Reference lists of papers were checked to maximise completeness. The causal relationship between drugs and development of acute pancreatitis was assessed according to a standard algorithm.*

***Results:** ACE-inhibitors, 5-ASA, asparaginase, azathioprine, codeine, didanosine, isoniazid, metronidazole, estrogens, pentavalent antimonials, beta-blockers, sulindac, tetracycline, and valproic acid had a definite causal relationship with acute pancreatitis; 34 other drugs had a probable causal relationship with acute pancreatitis.*

***Conclusions:** Drug-induced acute pancreatitis does not have unique features which distinguish it from acute pancreatitis due to other causes. A wide variety of drugs have been suspected of causing pancreatitis. Despite numerous case-reports on drug-induced acute pancreatitis, quantitative information on this subject is scanty. Formal epidemiological studies are needed to quantify the risk of drug-induced acute pancreatitis.*

## INTRODUCTION

Acute pancreatitis is an inflammatory disease of the pancreas characterized by abdominal pain, nausea, and vomiting. Laboratory examinations usually reveal elevated levels of serum amylase and lipase. Acute pancreatitis has an overall case-fatality of 5-10%,(1,2) but case-fatality can be as high as 40% in patients with infected necrosis of the pancreas.(3)

Gallstones and alcohol abuse are the most important risk factors for acute pancreatitis.(4) It has, however, since long been acknowledged that drugs may trigger acute pancreatitis.(5) Drug-induced pancreatitis has no unique features that distinguish it from acute pancreatitis due to other causes. Evidence linking drugs to acute pancreatitis is mostly derived from spontaneous reporting systems and individual case-reports in the medical literature. We conducted an extensive literature search to summarize the current knowledge about drug-induced acute pancreatitis.

## METHODS

We conducted a search using the terms drug-induced pancreatitis, drug-associated pancreatitis, chemically-induced pancreatitis, toxic pancreatitis, drug reaction pancreatitis, drug allergy pancreatitis and drug hypersensitivity pancreatitis in PubMed (including MEDLINE) during the period January 1966 – December 2001. We retrieved all English, German, French, and Dutch papers on acute pancreatitis associated with therapeutic or diagnostic drugs. Acute pancreatitis possibly related to calcium intake, parenteral feeding, or endoscopic retrograde cholangiopancreatography (ERCP) was not considered in this review. Reference lists of papers were checked to maximise completeness. Evidence from case reports and case series was assessed according to the algorithm in table 1. The temporal relationship was considered compatible with drug-induced acute pancreatitis if symptoms and signs had a reasonable temporal relationship to drug intake given the pharmacokinetics of the drug. Information from

**Table 1**  
Assessment of the causal relationship between a drug and development of acute pancreatitis

Criterion	Definite	Probable	Probable	Possible	Unlikely
Temporal relationship compatible	Yes	Yes	Yes	Yes	No
Other risk factors	No	No	NA		
Patients > 1	Yes	Yes	No		
Relapse after deliberate rechallenge	Yes		Yes		

NA = not assessed

animal, clinical, and observational studies was further used to classify the causal relationship between drugs and acute pancreatitis. This review focuses on reports with a certain or probable causal relationship.

## **LITERATURE REVIEW**

### **Antibiotics**

#### ***Ampicillin***

One patient experienced two episodes of acute pancreatitis 6 and 4 days after start of ampicillin. She had no other risk factors for acute pancreatitis.(6)

#### ***Ceftriaxone***

Ceftriaxone may induce sludge or small stones in the gallbladder.(7,8) Acute pancreatitis attributed to ceftriaxone-induced sludge or cholelithiasis has been described in 4 patients.(9-12) Analysis of gallstones derived after cholecystectomy showed the stones to be composed of ceftriaxone in two patients.(9,10) Imaging procedures failed to show sludge or stones in a fifth report of ceftriaxone-associated acute pancreatitis.(13) An association between ceftriaxone and acute pancreatitis is probable given ceftriaxone's capability to induce gallstones.

#### ***Macrolide antibiotics***

Five patients developed acute pancreatitis within 30 minutes to 3 hours after an oral overdose or after intravenous administration of a high dose of erythromycin.(14-18) Another patient developed multi-organ toxicity with rhabdomyolysis and pancreatitis after addition of erythromycin to long term lovastatin therapy.(19) Rhabdomyolysis was probably caused by increased serum-levels of lovastatin when erythromycin inhibited its metabolism. Acute pancreatitis attributed to the newer macrolides roxithromycin and clarithromycin has also been reported.(20,21) Erythromycin has a prokinetic effect on the smooth muscle of the gastrointestinal tract and the gallbladder(22) and may increase the pressure of the sphincter of Oddi.(17)

#### ***Nitrofurantoin***

Two cases of nitrofurantoin-induced acute pancreatitis have been described. (23,24) Both cases were confirmed by rechallenge: one by deliberate and one by inadvertent re-exposure. One patient had cholestatic liver disturbances.(23) The other patient used an oral contraceptive.(24) Nitrofurantoin-associated acute pancreatitis was further mentioned in a survey from a spontaneous reporting centre.(25)

### ***Sulfonamides***

Sulfonamide-associated acute pancreatitis has been described in case-reports (26-33) and is briefly mentioned in 3 studies.(34-36) An early paper reported meningitis and pancreatitis attributed to sulfamethizole on 2 occasions.(37) Antonow, et al. described a case of sulfamethoxazole-trimethoprim-associated acute pancreatitis. Although this patient used other medications associated with acute pancreatitis, prompt recurrence of symptoms after rechallenge suggested that sulfamethoxazole-trimethoprim was the causative agent.(38) Sulfonamide-associated acute pancreatitis is probably immune-mediated as relapse after rechallenge occurs rapidly and some patients had a positive lymphocyte transformation test (39) and accompanying rash or fever.

### ***Tetracyclines***

The earliest reports linking tetracycline and acute pancreatitis concerned patients who developed acute fatty liver of pregnancy after use of tetracycline.(40-42) Tetracycline-induced acute fatty liver and pancreatitis has been reported in 5 non-pregnant patients. In three, however, pancreatitis was present before tetracycline intake,(43) one had cholelithiasis,(44) and in the fifth patient, pancreatitis was detected at autopsy.(45) Acute pancreatitis after tetracycline intake without acute fatty liver has been described in 4 patients in whom other major risk factors for acute pancreatitis were absent.(46-48) Two of them experienced a relapse of pancreatitis after restart of tetracycline.(47,48) Acute pancreatitis associated with the use of minocycline has been reported in 5 patients,(49-51) although in one patient the development of pancreatitis was probably related to liver transplantation(50) and 2 other patients had cystic fibrosis.(51) Doxycycline-associated acute pancreatitis has been reported to the Dutch and Swiss reporting centres.(29,52) and in 2 clinical studies (2/54 and 9/72 patients respectively). (53, 54)

### **Anti-HIV agents**

#### ***Didanosine and other nucleoside analogues***

Didanosine (2',3'-dideoxyinosine) is a purine analogue with antiretroviral activity which has been associated with acute pancreatitis in case-reports (25,29,33,52,55-61) and clinical studies.(62-90) The cumulative incidence of pancreatitis in didanosine treated HIV-patients varied from 1 to 24% in different studies.(77,86) Risk factors for didanosine-induced acute pancreatitis are a history of acute pancreatitis,(73) advanced stage of HIV-disease,(80) use of pentamidine,(91) high plasma levels of didanosine,(91) and a high cumulative (79) or daily dose of didanosine.(87-89, 91) Hydroxyurea and ribavirin increase the active metabolite of didanosine (ddATP) and acute pancreatitis after addition of ribavirin and hydroxyurea to didanosine therapy has been reported in several patients.(92-94) One study reported a relative risk of 8.6 (95% CI 1.9-39.4) for

adding hydroxyurea to didanosine, (95) although another study could not substantiate this.(96) Acute pancreatitis in sickle cell patients receiving hydroxyurea monotherapy has been reported.(97)

Relapse after rechallenge to didanosine has been described,(75) but such patients may respond favourably to dose reduction.(79) Acute pancreatitis has not been reproduced in animal studies.(98,99) Didanosine-induced hyperlipidemia has been proposed as a possible mechanism,(100) but mitochondrial toxicity is a more likely explanation.(101) The assessment of a causal relationship with didanosine is complicated by the association between HIV itself and acute pancreatitis,(26,102) and by the use of other drugs associated with acute pancreatitis, notably pentamidine and trimethoprim/sulfamethoxazole. However, a consistent time relationship between intake of didanosine and symptoms (12-18 weeks), dose dependency, and positive rechallenges point to a definite causal relationship. The capacity of didanosine to induce mitochondrial toxicity is shared by other nucleoside analogues, (101) and acute pancreatitis attributed to these agents has been described.(103-106) Indeed, similar incidences of acute pancreatitis have been observed in didanosine and zalcitabine users.(107)

### ***HIV-protease inhibitors***

Ritonavir is capable of inducing gross hypertriglyceridemia.(108,109) Acute pancreatitis due to HIV-protease-inhibitor-associated hypertriglyceridemia has been described in 8 patients 1-8 months after start of ritonavir or saquinavir.(109-114) Nelfinavir-associated pancreatitis with a positive rechallenge has been described in a non-alcoholic HIV-infected patient without cholelithiasis. However, the patient was on didanosine during the first attack and had normal levels of triglycerides on the first and second attack of pancreatitis.(115)

### **Other anti-infective agents**

#### ***Antitubercular agents***

Five patients experienced acute pancreatitis after starting antitubercular therapy including isoniazid, in whom a relapse occurred in three after readministration.(116-120)

Chan, et al. reported no cases of pancreatitis in 6024 isoniazid/rifampicin treated patients, suggesting that the absolute risk of acute pancreatitis in patients receiving these medications is low.(121)

#### ***Fialuridine***

In a study on the treatment of chronic hepatitis B with fialuridine (FIAU), 7 out of 15 patients developed severe hepatotoxicity after 9-13 weeks of therapy.(122) All

7 had elevated lipase levels, all 5 patients who died had evidence of pancreatitis at autopsy. Three patients had mild fialuridine-induced toxicity, of whom one had elevated pancreatic enzyme levels and epigastric discomfort. Toxicity was probably mediated by FIAU-induced mitochondrial injury.(123) The similarities in the clinical picture and temporal relationship between start of treatment and start of symptoms in these 7 patients, suggests a causal relationship between FIAU and acute pancreatitis/hepatitis.

### ***Interferon***

Acute pancreatitis attributed to interferon has been described in two children (124,125) and in 8 adult patients. (25,126-129) In three of them acute pancreatitis returned upon rechallenge with interferon. However, one patient used up to 5 units of alcohol per day, one had sludge in the gallbladder,(129) and in one the information was scanty.(128) A patient with adult T-cell leukaemia (ATL) experienced acute pancreatitis shortly after start of interferon therapy,(130) but this episode was probably provoked by ATL associated hypercalcemia.(131). In a study on fluorodeoxyuridine, leucovorin and interferon treatment in patients with metastatic renal-cell cancer two developed pancreatitis.(83,132)

### ***Metronidazole***

An association between metronidazole and acute pancreatitis has been suggested in 6 case reports.(133-138) Four patients experienced a relapse of pancreatitis after inadvertent re-exposure to metronidazole.(133-136) The fifth patient had used numerous other medications, but apart from metronidazole all drugs had been used for at least 36 months.(137) Crohn's disease may have played a role in the development of acute pancreatitis in this last patient.(139-141) Among 6485 users of metronidazole, none were hospitalised for acute pancreatitis within one month of treatment.(142) This is, however, not surprising: if one assumes an incidence rate of 25/100,000 person-years in the general population, and a relative risk of 5 for metronidazole, the number of cases that one would expect to find would be 0.7.

### ***Pentamidine***

Pentamidine is frequently used in patients with HIV-disease. Twenty-seven patients with pentamidine-associated acute pancreatitis have been reported, 14 of whom died.(29,143-164) Acute pancreatitis developed mostly within 2-3 weeks after starting treatment. Relapse of pancreatitis after re-exposure has been reported (159,160) but both patients had also used trimethoprim-sulphamethoxazole. Acute pancreatitis after aerosolised pentamidine has also been reported.(161-163) Pentamidine-associated acute pancreatitis has been reported in clinical studies.(34-36,62,165,166) *Mycobacterium avium intracellulare*, age, gallstones, and use of pentamidine are risk

factors for development of pancreatitis/hyperamylasemia in patients with HIV infection.(167-169) Renal impairment has been proposed as an additional risk factor since pentamidine is excreted by the kidneys.(157) One animal experimental study found pancreatitis in pentamidine infused rats only if they had undergone bilateral nephrectomy.(170) Pentamidine accumulates in the pancreas where it can be found up to 1 year after stopping treatment,(171) and pentamidine was detectable in serum samples up to 2-4 weeks after end of therapy.(150,164) Pentamidine has a cytotoxic effect on pancreatic isle  $\beta$ -cells (35) and may possibly have the same effect on acinar pancreatic cells.

### ***Pentavalent antimonials***

There are numerous reports on pentavalent antimonials and acute pancreatitis.(172-187) Of the 12 patients described in case-reports, 6 were treated with stibogluconate and 6 were treated with meglumine antimoniate.(172-179) Five patients were HIV-positive, four patients had received a renal transplant, conditions which are associated with an increased risk of pancreatitis.(102,188-190) Out of 7 patients treated with meglumine antimoniate, 4 developed hyperamylasemia.(182) Three patients experienced symptomatic pancreatitis during 46 treatment episodes with pentavalent antimonials.(183) In another study, 5 out of 25 patients treated with meglumine antimoniate experienced acute pancreatitis. None of them abused alcohol or had cholelithiasis.(184) In the period 1989-1996, 96 patients with leishmaniasis were treated with stibogluconate in the Walter Reed Army Medical Center (WRAMC). Over 95% of the patients had elevated amylase or lipase values, 30% had abdominal pain, and in 15 patients treatment was temporarily interrupted because of chemical or symptomatic pancreatitis. Most patients tolerated reintroduction of stibogluconate well. Pancreatic abnormalities tended to occur early in therapy and declined despite continuation of treatment.(185) An earlier report of the WRAMC showed elevated pancreatic enzyme levels in 32 Peruvian patients, of whom 11 had symptoms of pancreatitis. Treatment with pentavalent antimonials was continued in all 32 patients.(186) The latter studies suggest that acute pancreatitis is a frequent adverse-effect of pentavalent antimonials therapy that does not necessarily require treatment withdrawal.

## **Cardiovascular agents**

### ***Angiotensin converting enzyme inhibitors (ACE-inhibitors)***

Captopril, enalapril, lisinopril, perindopril, benazepril, and quinapril have all been associated with acute pancreatitis.(25,52,191-210) Three patients experienced a relapse after restart of captopril, enalapril, and perindopril respectively.(191-193) One other patient possibly experienced pancreatitis after previous exposure to lisinopril.(206) The incidence of lisinopril-associated acute pancreatitis in clinical trials is

0.3-1.0%.(201) Pancreatic duct obstruction by local angioedema may be the mechanism by which ACE-inhibitors cause pancreatitis.(198) Others have proposed a direct toxic effect on pancreatic cells.(199) Because captopril is structurally dissimilar to enalapril and lisinopril, an allergic reaction seems less likely.(198).

### ***Losartan***

Two patients experienced pancreatitis after intake of losartan, and in both patients the association was confirmed by a positive reaction to rechallenge. (211,212) One had renal insufficiency, the other had used enalapril up to 4 days before the first attack and atenolol up to 3 days before the second attack. Noteworthy is that one patient had a recent history of enalapril-related cough,(212) and that the other patient had a recent history of enalapril-associated acute pancreatitis.(211)

### ***Antiarrhythmic drugs***

Two cases of amiodarone-associated acute pancreatitis have been described. One patient had fatal hepatotoxicity with epigastric pain and mildly elevated amylase and lipase serum levels after 3.5 years of therapy, but this patient had an unremarkable CT-scan.(213) In the other patient, the relationship between amiodarone and pancreatitis was confirmed by recurrence of pancreatitis after rechallenge, which makes an association probable.(214)

Acute pancreatitis related to procainamide has been described in 2 patients. Both patients had procainamide-induced lupus syndrome.(215,216) One had recurrence of symptoms after inadvertent re-exposure.(215)

### ***Diuretics***

One of the few epidemiological studies on drug-associated acute pancreatitis showed a significant excess of diuretic users – mostly cyclopenthiiazide - among patients with pancreatitis. (217) A subsequent study was suggestive of a threefoldly increased risk.(218) Many reports of acute pancreatitis to thiazides,(29,219-229) and the related compounds chlorthalidone, metolazone, and indapamide have been reported.(29,228,230-234) One patient developed a relapse of pancreatitis after restart of methychlothiazide/triamterene combination therapy.(229) Hypercalcemia induced by thiazides could theoretically explain the association. However, elevations of serum calcium are usually mild, transient, and asymptomatic.(235) A study in 300 mice treated with chlorothiazide, showed acute pancreatitis in 7.1%.(236)

Acute pancreatitis has been associated with furosemide in several patients.(25,34,237-242) Three had a relapse of pancreatitis after rechallenge with furosemide. The first patient had type II hyperlipidemia and had received morphine.(239) The second patient had gross hyperlipidemia and used estrogens upon admission. She was challenged in normolipemic state with estrogen, which she tolerated well and with furo-

semide, after which she relapsed.(238) The third patient was known with renal failure and malignant hypertension. He developed acute pancreatitis twice after furosemide intake and hyperamylasemia after subsequent bumetanide intake.(240)

### ***Methyldopa***

Five cases of methyldopa-associated acute pancreatitis have been described,(243-246) of which 4 were confirmed by rechallenge.(243-245) Although most patients used other medications that have been associated with acute pancreatitis and 1 patient had cholelithiasis,(244) a causal relationship between methyldopa and acute pancreatitis is highly probable.

### ***β-Blockers***

A 64-year-old man developed marked hyperlipidemia with pancreatitis by reduced clearance of lipids after starting atenolol.(247) One patient developed hyperlipidemia with secondary acute pancreatitis after exposure and re-exposure to nadolol.(248) Other cases of hyperlipidemia by β-blockers have been reported.(249,250)

## **Gastrointestinal agents**

### ***5-ASA***

The literature on aminosalicylate-associated acute pancreatitis is abundant.(25,245,251-279) Both sulfasalazine (25,245,251-260) and mesalazine (25,253,258-280) have been implicated. The first reports on sulfasalazine suggested that the sulfapyridine moiety was responsible for this adverse effect. Cross-reactivity between sulfasalazine and mesalazine(258-260) and the numerous reports on mesalazine-associated pancreatitis has shifted the attention to the aminosalicylates. One should take into account that inflammatory bowel disease itself is associated with acute pancreatitis,(139-141) and that several patients used other medications that have been associated with acute pancreatitis (prednison, azathioprine) or had other risk factors for acute pancreatitis. Even so, the large number of recurrences of pancreatitis after rechallenge demonstrate a definite relationship between aminosalicylates and acute pancreatitis.(25, 255-268), one of which after rectal rechallenge (258) Aminosalicylate-associated acute pancreatitis is probably immune-mediated as rechallenge with small doses can produce relapses of acute pancreatitis within hours and because lymphocyte transformation tests were positive in one patient.(275)

### ***Diphenoxylate/atropine***

A 62-year-old woman developed acute pancreatitis within 3 hours of taking diphenoxylate/atropine on 2 separate occasions. There were no other risk factors for acute pancreatitis.(281)

## ***H2-Blockers***

Cimetidine has been associated with pancreatitis in six cases.(52,282-285) The association was confirmed by a deliberate rechallenge in 2 patients,(284) and inadvertent re-exposure in two others.(52,283) Relapse of pancreatitis after inadvertent re-exposure with cimetidine and a case of famotidine-associated pancreatitis are mentioned in a study of spontaneous reports to a national monitoring centre of adverse drug reactions.(52) An 81-year-old woman experienced three bouts of acute pancreatitis after (re)start of ranitidine.(286) One study suggested that cimetidine may cause acute pancreatitis in rats,(287) but others have questioned this.(288,289) Two observational studies found an elevated risk of acute pancreatitis for H2-blockers, albeit non-significant. (290,291) In assessing a relationship between H2-Blockers and acute pancreatitis one has to bear in mind that acid-suppressing drugs may be prescribed for prodromal symptoms of acute pancreatitis.

## ***Somatostatin analogues***

Nine patients experienced acute pancreatitis while on the somatostatin analogues octreotide and lantreotide. (292-298) One patient already had an enlarged pancreas before start of therapy, (294) 2 were HIV-positive (292,293), 2 had relapsing acute pancreatitis before start of therapy, (295), one had pancreatitis only on octreotide-codeine therapy and not on these drugs apart, (295) and in 1 patient with rechallenge the information was very scanty. (297) Deliberate rechallenge in 3 patients resulted in a relapse of acute pancreatitis. (293,296) However, symptoms settled and amylase normalised while treatment was continued in 2 other patients. (296,298) Numerous hypotheses regarding the mechanism of somatostatin have been proposed, but increased contractility of the sphincter of Oddi seems to be the most plausible. (293,296) Sphincter of Oddi manometry showed a higher frequency of Oddi contractions after octreotide administration in 6 patients with idiopathic recurrent pancreatitis. Pancreatitis developed in 5 of them after the procedure.(299) Most of above described patients developed acute pancreatitis within hours, which is compatible with this hypothesis. Long-term octreotide therapy is associated with cholelithiasis. (300,301)

## **Immunosuppressives and antineoplastic agents**

### ***Asparaginase***

Asparaginase is an anti-neoplastic drug that has been associated with acute pancreatitis since more than 30 years.(302) Evidence from case-reports, however, is anecdotal and other risk factors for acute pancreatitis were not always excluded.(29,34,303-328) Most patients received other drugs, notably prednisolone and vincristine. Recurrence of pancreatitis after rechallenge has not been described. Most cases pertain to asparaginase derived from *Escherichia coli* (319,329) but pancreatitis associated with

asparaginase derived from *Erwinia chrysanthemi* has also been reported (327) and seems to have a lower incidence. (330) Another patient experienced several adverse reactions, among which pancreatitis after a single injection of 1000 IU/kg. Rechallenge at half the dose several months later was well tolerated.(326) The cumulative incidence of acute pancreatitis in studies of patients treated with asparaginase averages around 5-10%.(302,329,331-346) Another study found a higher incidence in polyethylene glycol-L-asparaginase than in native *E. Coli* asparaginase (9/50 vs. 1/50) Weetman, et al suggested a role for estrogens as most of their patients were pubertal females.(337) Interestingly, a study on rat liver asparaginase activity reported higher activity in female than in male rats. Asparaginase activity decreased after gonadectomy in female rats.(347) Asparaginase-induced hypertriglyceridemia has also been proposed as a possible mechanism.(328) Indeed a study on lipid abnormalities during asparaginase therapy found triglyceride levels of more than 11 mmol/l in 7 out of 38 patients. However, pancreatitis developed in 4 patients and all had normal triglyceride levels.(346) Serial ultrasound examinations have been proposed for early detection of asparaginase-induced acute pancreatitis, but results of this strategy are equivocal.(341,348)

### ***Azathioprine/6-mercaptopurine***

Numerous case-reports linking azathioprine,(25,29,52,349-364) and its metabolite 6-mercaptopurine (364-367) to acute pancreatitis have been published, the majority with recurrence of pancreatitis after rechallenge.(25, 357-365) In addition, acute pancreatitis has been described in patients with systemic lupus erythematosus,(368,369) and in patients with renal transplants on immunosuppressive therapy that included azathioprine.(188,190,370-373) The occurrence of symptoms within weeks after starting azathioprine therapy, recurrence of symptoms within hours after rechallenge, and dose independency suggest an immune-mediated reaction. One report mentioned among others acute pancreatitis after addition of allopurinol to azathioprine therapy, possibly due to impairment of azathioprine/mercaptopurine breakdown by xanthine-oxidase.(374) Both synergistic and protective effects of concomitant prednisone therapy have been suggested.(357,375) In a randomised trial comparing azathioprine, prednisone, sulfasalazine, and placebo, 6 (5.3%) patients in the azathioprine group developed acute pancreatitis versus none in the other 3 groups. Four of them reported prompt recurrence of symptoms after self-initiated stop and restart of azathioprine intake.(376) Another study reported acute pancreatitis in 12 out of 400 patients treated with immunosuppressive therapy that contained 6-mercaptopurine for inflammatory bowel disease. All 7 patients that were rechallenged developed a relapse of pancreatitis, some on very small dosages.(377) Azathioprine-induced pancreatitis is mentioned in several other azathioprine/6-mercaptopurine safety reports (375,378-380) and clinical reports (53, 381) but has not been reproduced in two animal

studies (382,383). One study advocates weekly laboratory examination during the first 2 months of therapy to detect elevated levels of amylase before pancreatitis becomes clinically manifest.(384)

### ***Combination chemotherapy***

One patient developed acute pancreatitis after the 5th and 6th course of vincristine, methotrexate, mitomycin, 5-FU and cyclophosphamide.(385) A second patient developed acute pancreatitis after the 2nd, the 3rd, and the 4th treatment cycle with cyclophosphamide, doxorubicin, vincristine and prednisone.(386) Similar cases have been reported ,(387) one which was able to continue chemotherapy after substituting vinblastine with etoposide. Noteworthy is that vinblastine or vincristine were included in all these regimens as an animal study found marked autophagy after high dose vinblastine/vincristine.(388)

### ***Corticosteroids***

Oral cortisone is the first drug for which a potential causal relationship to acute pancreatitis was considered.(389) Since then, over 50 case-histories have been published.(29,368,370,373,390-417) and corticosteroid-associated acute pancreatitis is briefly mentioned in several case-series.(53,54,381,418-421) Interestingly, acute pancreatitis in patients with Cushing's disease has also been reported.(422,423) As 2 critical reviews have pointed out, however, most reports on corticosteroid-induced pancreatitis do not firmly support a causal relationship.(424, 425) Autoimmune disorders, hypercalcemia, history of alcohol abuse, or cholelithiasis was noted in some reports and may have been causative. There is no apparent time relationship and rechallenge data are scanty. An HIV-positive patient with a history of didanosine-associated pancreatitis developed pancreatitis after 2 days of prednisone therapy. He again experienced an episode of pancreatitis 2 weeks later after 1 day of dexamethasone therapy. (395) Another patient had a rise of serum amylase after restart of 30 mg prednisolone, but amylase values normalised after lowering the dose of prednisone.(410) One patient experienced 3 episodes of acute pancreatitis 2-6 days after start of dexamethasone, but had a history of alcohol abuse.(409) Two autopsy studies found higher prevalences of pancreatic lesions in patients treated with steroids.(416,426) One compared deceased patients before and after 1955,(416) the other compared deceased patients who had used steroids to a matched control group that had not used steroids.(426) Studies on the influence of corticosteroids on secretory function of the pancreas are conflicting.(427,428) Studies in steroid treated rabbits have shown peripancreatic fat necrosis and mild pancreatic changes.(429, 430) Studies in dogs have been less successful in inducing pancreatic lesions.(431-433) In one study, 5/31 methylprednisolone treated patients versus 10/103 non-treated patients developed acute pancreatitis, (434) but another study was negative.(435) Given the inconclusive evidence described above,

we conclude that the association between corticosteroids and acute pancreatitis is questionable.

### ***Cytarabine***

Acute pancreatitis attributed to cytarabine has been described several times.(29,436-441) One patient developed acute pancreatitis after continuous infusion of cytarabine. Rechallenge with intermittent high-dose cytarabine was well tolerated. Subsequent rechallenge with continuous infusion led to relapse of acute pancreatitis. An ultrasound 17 days later showed sludge in the gallbladder.(436) Altman, et al. described the case of a 14-year-old boy who developed acute pancreatitis on the 3rd cycle of cytarabine maintenance regimen. He developed abdominal pain on the 4th cycle, which was not further investigated, and he experienced a relapse of pancreatitis on the 5th cycle.(438) Two cases-series mention acute pancreatitis in 2/25 and 3/93 patients treated with cytarabine.(439, 440) A third study showed pancreatitis in 7 out of 137 patients.(441) One out of the 5 patients in whom treatment was continued experienced a relapse of pancreatitis.

### ***Ifosfamide***

One patient experienced two episodes of acute pancreatitis within 24 hours after the 2nd and 4th dose of ifosfamide.(442) She had abdominal pain after the 1st cycle. An ultrasound showed sludge during the first attack of acute pancreatitis. Another patient developed a petechial rash after 2 days ifosfamide treatment. Two days later she developed acute pancreatitis without presence of conventional risk factors.

## **Neuropsychiatric agents**

### ***Clozapine***

There are several reports on clozapine-associated acute pancreatitis.(443-450) However, 3 patients had no abdominal pain.(443-445) One patient had a return of abdominal pain after restart of clozapine. Amylase values were not reported during this relapse and she had used valproate before her first attack.(446) Another patient relapsed twice after consecutive restarts of clozapine, but this patient had concomitant cholelithiasis.(447)

### ***Pyritinol***

A 23-year-old male experienced 3 episodes of acute pancreatitis.(451) The time between start of pyritinol decreased from 3 months to 6 and 4 days respectively. He was rechallenged with a single dose of pyritinol and developed a relapse of acute pancreatitis within 3 hours. A lymphocyte stimulation test was positive for pyritinol.

### ***Valproic acid***

The antiepileptic drug valproic acid has been associated with acute pancreatitis in over 40 patients.(29,452-486). Most cases concerned children, which is consistent with the prescription pattern of valproic acid. Acute pancreatitis usually develops in the first year of therapy, but delayed onset of acute pancreatitis has been described.(462) After restart of valproic acid, 8 patients had recurrence of pancreatitis. Four patients tolerated restart of valproic acid: one on the original dose, one on a lower dose, and 2 after renal transplantation.(452-462) One patient developed chronic pancreatitis while on valproic acid.(487) Although acute pancreatitis after intoxication with valproic acid has been described,(480,486) most patients had serum levels within the therapeutic range. It has been postulated that valproic acid causes acute pancreatitis by inhibiting detoxification of free radicals. Valproic acid enhances the clearance of selenium, copper, and zinc. These trace elements are essential for the functioning of radical scavengers.(485) One toxicity study in rats showed atrophic pancreatitis after 52 weeks of valproic acid intake.(488) The incidence of valproic acid-associated acute pancreatitis is unknown. In a survey among physicians with an interest in epilepsy, 14.5% of respondents indicated they had encountered pancreatitis attributed to valproic acid.(462) Out of 100 children that were treated with valproic acid, one developed acute pancreatitis.(489) Out of 78 patients with renal failure, 4 developed acute pancreatitis. All 4 were valproic acid users, while none of the other 74 patients used valproic acid.(461)

### **Miscellaneous drugs**

#### ***Bezafibrate***

A 75-year-old woman was hospitalised with fever and confusion 3 weeks after starting bezafibrate for mild hypercholesterolemia.(490) She was readmitted two times for acute pancreatitis within hours of taking bezafibrate. She had no other risk factors for acute pancreatitis.

#### ***Codeine***

The first report of acute pancreatitis by codeine dates back to 1951 in a patient who had recurrent episodes of pancreatitis for many years.(5) Deliberate rechallenge with codeine sulphate on 2 separate occasions was followed by recurrence of pancreatitis on both occasions. Elevated levels of pancreatic enzymes were found in 5 other patients after deliberate exposure to codeine sulphate, of whom 3 had concurrent abdominal pain.(5) Since this first report, pancreatitis attributed to codeine has been described in several other patients. (491-494) In one the diagnosis was by no means sure (491,492) In 3 others inadvertent rechallenge with codeine was followed by a relapse of acute pancreatitis within hours.(493) This short induction time is compatible with a hypoth-

esis of biliary obstruction by spasm of the sphincter of Oddi.(5,495) In 2 of the patients acute pancreatitis developed after intake of paracetamol-codeine.(493,494)

### ***Estrogens***

Estrogen-associated pancreatitis has been described in women taking oral contraceptives,(233,496-508) in post-menopausal women taking hormonal replacement therapy,(509-511) and in men taking estrogens for prostate-related problems.(511,512) Most patients had severe estrogen-induced hypertriglyceridemia.(502-512) However, estrogen-associated acute pancreatitis without hyperlipidemia has also been described.(497,498) Thrombosis in pancreatic vessels has therefore been proposed as a potential mechanism.(497,513) Two patients had relapse of pancreatitis after restart of oral contraceptive therapy.(501,505) Three other patients had multiple attacks of acute pancreatitis while on contraceptive therapy.(505-507) In a case-series, estrogen-induced acute pancreatitis was suspected in 15 out of 73 patients.(54) An experimental study in rats found hemorrhagic pancreatitis in female and male oestradiol treated rats given a choline deficient, ethionine enriched diet, but not in control rats.(514) In a study of 31 women with hypertriglyceridemia, 12 used hormonal replacement therapy. After cessation of therapy, start of a low fat diet, and start of gemfibrozil therapy, lipid levels decreased sharply.(515) Estrogens are definitely associated with acute pancreatitis given the fact that estrogens are capable of inducing gross hypertriglyceridemia in susceptible patients,(516) and given the return of symptoms after restart of estrogens in 2 patients. Transdermal oestradiol therapy may be an option in patients with pre-existing hypertriglyceridemia.(517)

Tamoxifen and clomiphene are synthetic estrogen analogues with mixed agonist-antagonist actions. Two patients with pre-existent familial hyperlipidemia developed gross hyperlipidemia with subsequent acute pancreatitis after 4 and 8 months of tamoxifen therapy for breast cancer. Other major risk factors for acute pancreatitis were not described.(518,519) Tamoxifen-induced hypertriglyceridemia without pancreatitis has been described before.(520) Acute pancreatitis secondary to clomiphene-associated hypertriglyceridemia has been described in a 37-year-old woman. Restart of clomiphene led to severe hypertriglyceridemia with a subsequent relapse of pancreatitis.(521) Cholelithiasis could possibly explain development of acute pancreatitis in another patient on clomiphene.(233)

### ***Fenfluramine***

Dexfenfluramine and fenfluramine have been associated with acute pancreatitis in 2 reports.(522,523) One of these patients had a history of acute pancreatitis 11 years earlier, which was preceded by intake of fenfluramine.(523) The other patient had numerous other medications but these had been used for over 5 years and were re-introduced after attenuation of symptoms without any problems.

### ***Growth hormone***

A 12-year-old boy developed acute pancreatitis after his 6th dose of growth hormone. After rechallenge acute pancreatitis returned promptly.(524) Other risk factors were not described, but alcohol abuse and gallstones are rare in children. More cases were reported to the manufacturer (525) and the FDA (524).

### ***HMG CoA reductase inhibitors***

One patient developed pancreatitis one week after start of lovastatin.(526) Six months later lovastatin was restarted with prompt recurrence of abdominal symptoms. Unfortunately, serum amylase values were not assessed at that time.

Five patients developed acute pancreatitis between 12 hours and 7 months after start of simvastatine therapy.(527-530) One of them stopped simvastatine intake after 7 months on his own initiative because of abdominal pain. After restart, symptoms recurred in 7 days. One study from a spontaneous reporting centre mentioned a rechallenge proven simvastatine-associated acute pancreatitis and fluvastatine-associated pancreatitis in another patient. However details were not provided.(25) In one patient acute pancreatitis developed 8 hours after start of atorvastatine.(531) Two patients developed rhabdomyolysis with concurrent pancreatitis after simvastatine and lovastatin-gemfibrozil therapy.(532,533)

### ***Methimazole***

A 66-year-old woman with Graves' disease experienced acute pancreatitis and parotitis 3 weeks after starting methimazole.(534) She had elevated levels of salivary and pancreatic amylase, and lipase. She developed a relapse of pancreatitis within 3 hours after rechallenge.

### ***Non steroidal anti-inflammatory drugs (NSAIDs)***

In NSAID-associated acute pancreatitis, sulindac seems to stand out.(535-542) Seven out of the 10 patients had a relapse of pancreatitis after rechallenge.(536-542) Seven patients had cholestatic liver function test disturbances in absence of cholelithiasis.(535-539,543) This can possibly be explained by sulindac-induced bile duct injury.(538) Indomethacin,(544) ibuprofen,(52,545), tolfenamic acid,(29) mefenamic acid,(245,546) oxyphenbutazon,(547,548) phenylbutazon,(25) piroxicam,(29,549,550) tiaprofenic acid,(551) ketoprofen, (552-554) diclofenac,(233,550,555) naproxen, (550,556,557) and ketorolac (558) have sporadically been associated with acute pancreatitis. Recently, two cases of pancreatitis attributed to the cyclooxygenase-2 selective NSAID celecoxib have been described.(559,560) Both patients used other drugs previously associated with acute pancreatitis. In assessing the relationship between NSAIDs and acute pancreatitis, one has to consider the possibility of protopathic bias: the prescribing of drugs for prodromal symptoms of acute pancreatitis. Sulindac, how-

**Table 2**

Drugs with a definite or probable causal relationship to acute pancreatitis

Definite	Probable	Probable
5-ASA	Amiodarone	Losartan
ACE-inhibitors	Ampicillin	Macrolide antibiotics
Asparaginase	Bezafibrate	Mefenamic acid
Azathioprine/mercaptopurine	Ceftriaxone	Methimazole
Codeine	Clozapine	Methyldopa
Didanosine (ddl)	Cytarabine	Naproxen
Isoniazid	Diphenoxylate	Nitrofurantoin
Metronidazole	Fenfluramine	Oxyphenbutazone
Estrogen compounds	Fialuridine	Pentamidine
Pentavalent antimonials	Furosemide	Procainamide
$\beta$ -Blockers	Growth hormone	Propofol
Sulindac	H2-Blockers	Pyritinol
Tetracycline	HIV-protease inhibitors	Retinoids
Valproic acid	HMG CoA reductase inhibitors	Somatostatin analogues
	Ifosfamide	Sulfonamides
	Interferon	Thiazides
	Ketoprofen	Vitamin D

ever, is a definite cause of pancreatitis. For naproxen, ketoprofen, mefenamic acid, and oxyphenbutazon the causal relationship with acute pancreatitis is probable.

### ***Propofol***

Five cases of propofol-associated acute pancreatitis have been reported in the literature.(561-565) One patient had a relapse of pancreatitis after inadvertent re-exposure to propofol during surgery, but this patient had concomitant cholelithiasis.(561) One further patient has been reported who developed elevated pancreatic enzyme levels after propofol therapy in a patient with severe head injury.(566) However, head trauma in itself is associated with elevated amylase levels.(567,568) Several other cases have been reported to the FDA.(562,569) A recent study on propofol infusion in rats showed an increase of lipid levels in rats on continuous infusion. Three rats in the continuous infusion group (n = 30) developed histological pancreatitis versus 1 in the control group and none in the bolus infusion group.(570) Two randomised controlled trials showed no differences in serum lipase and amylase,(571,572) slightly elevated triglyceride levels were found in one study.(572)

### ***Retinoids***

Six patients have been described with hyperlipidemia and secondary pancreatitis after use of retinoids for leukaemia and dermatological disorders.(573-578) One patient had type IV hyperlipidemia and used estrogens, which are known to produce hyperlipidemia.(576) Two other patients also had pre-existent hyperlipidemia.(573,577) One

**Table 3**

Drugs with a possible causal relationship to acute pancreatitis

Possible		
Alendronate (52,586)	Famotidine (see text)	Mycophenolate mofetil(587)
Allopurinol(25)	Felodipin(29)	Nicotine(588)
Amineptine(589)	Finasteride(590)	OKT3(591)
Aminophylline(415)	Floxuridine/mitomycin C(592)	Olanzapine(593-596)
Amoxapine(25,597)	Fluconazol(29)	Ondansetron(598)
Anticholinesterase agent(599)	G-CSF(600)	Oxcarbazepine(25)
Aspirin(601)	Glicazide(602)	Paclitaxel(603,604)
BHI regeneration tablets(605)	Gold(606,607)	Paracetamol(25,29,52,245,608-613)
Bromide(614)	Granisetron(615)	Paromomycin(616)
Carbamazepine(617-619)	Griseofulvin(25)	Penicillin(620)
Celecoxib (see text)	Histamine(621)	Pentagastrine(622)
Chlormezanone(623)	Hydroxyurea (97)	Phenacetin(624)
Cholestyramine(25,625)	Ibuprofen (see text)	Phenformin(626-632)
Ciprofibrate(52)	Imipenem(633)	Phenolphthalein(634)
Ciprofloxacin(635)	Imipramine(25)	Phenprocoumon(29)
Cisplatin(636-638)	Indalpine(639)	Phenylbutazon (see text)
Clofibrate(640-642)	Indomethacin (see text)	Piroxicam (see text)
Clomipramine(25,643)	Interleukin 2(644)	Propylthiouracile(645)
Clonidine(646)	Itraconazol(647)	Ribavirin(648)
Colchicine(649,650)	Ketorolac (see text)	Rifampicin(583,651-653)
Corticosteroids (see text)	Lamivudine(654)	Riluzole(655,656)
Cyclophosphamide(368,396)	Lamotrigine/vigabatrin(657)	Risperidone(658,659)
Cyclosporine(29,660-663)	Linomide(664)	Tacrolimus(665-667)
Dapsone(668)	Lithium(25)	Thalidomide(669)
Diazoxide(670,671)	Loperamide(672,673)	Tiaprofenic acid (see text)
Diclofenac (see text)	L-tryptophan (674)	Ticarcillin/clavulanic acid(675)
Diethylpentenamide(676)	Maprotiline(52)	Ticlopine(25)
Donepezil(677)	Metaraminol(678)	Tolfenamic acid (see text)
Ergotamine(679)	Metformin(680)	Triciribine(681)
Ethacrynic acid(682,683)	Methandienone(684)	Ursodeoxycholic acid(685)
Ethchlorvynol(686)	Methotrexate(368)	Vinorelbine(687,688)
Exatecan mesylate(689)	Methylphenidate(690)	Warfarin(691)
Famciclovir(692)	Morphine(693-699)	

patient experienced 2 episodes of acute pancreatitis 2 years apart, after intake of isotretinoine, but this patient had concomitant sludge and cholelithiasis.(578) Acute pancreatitis due to bexarotene (a retinoid-X-receptor selective retinoid) induced hypertriglyceridemia is mentioned 2 clinical trials.(579,580)

### ***Vitamin D***

Acute pancreatitis developed in a patient with hypercalcemia due to cholecalciferol and calcium supplements. Unfortunately, information on other major risk factors for acute pancreatitis was not provided.(581) Another patient had a vitamin D concentration that was 4.5 times the normal level and hypercalcemia during his fourth admission for acute pancreatitis. On questioning, the patient admitted intake of massive

amounts of vitamin D. He did not have any other risk factors for acute pancreatitis, and neither patient had hyperparathyroidism.(582) Interestingly, the patient had elevated levels of vitamin D for up to 3 months after stopping vitamin D intake. This is probably due to mobilisation of stored vitamin D from tissues. Vitamin D is probably related to acute pancreatitis, most likely by inducing hypercalcemia.

Drugs with a definite or probable causal relationship to acute pancreatitis are summarised in table 2. Drugs with a possible causal relationship are listed in table 3.

## DISCUSSION

Over 150 drugs have been proposed as a potential cause of acute pancreatitis. Evidence associating drugs with acute pancreatitis is largely based on individual case histories in which a close temporal relationship between drug intake and acute pancreatitis may be a chance finding. Relapse of pancreatitis after controlled rechallenge confirms a causal relationship. Such proof is uncommon, however, as rechallenge is only ethical when it concerns a drug which is essential for the treatment of the patient.

In some conditions, drug effects may be difficult to separate from the underlying condition. Mesalazine, azathioprine, and corticosteroids, for instance, are used in the treatment of inflammatory bowel diseases which itself increases the risk of acute pancreatitis. Protopathic bias may further complicate assessment of the causal relationship between drugs and acute pancreatitis. Two case-control studies found a non-significantly increased risk of pancreatitis among acid suppressing drug users, which could possibly be due to prescription of acid-suppressing drugs for prodromal symptoms of acute pancreatitis.(290,291) Despite these problems, clinical evidence strongly suggests a causal relationship for a number of drugs. Didanosine-induced acute pancreatitis, for instance, was reported as soon the first dose escalating studies were performed and it has consistently been reported since then. For some drugs a causal relationship with acute pancreatitis is certain despite a low incidence. The causal relationship between ACE-inhibitors, azathioprine, and metronidazole for instance has been confirmed by several well-documented rechallenges.

The pathogenesis of drug-induced acute pancreatitis is incompletely understood. Drugs or drug metabolites may theoretically have a direct toxic effect on the pancreas. Among the NSAIDs, sulindac seems to stand out in its ability to induce pancreatitis. The delay between start of sulindac and development of symptoms is several weeks to months, and after rechallenge symptoms reappear within days to weeks. This is compatible with a toxic effect on the pancreas. Didanosine-associated acute pancreatitis usually develops 10-18 weeks after start of therapy, which is well compatible with didanosine-induced mitochondrial toxicity.(101) For other drugs, an immunoallergic

idiosyncratic reaction is more likely. Time between start of treatment and development of pancreatitis is usually within a few weeks for mesalazine, azathioprine, methyldopa and sulfonamides. Rechallenge with these drugs usually leads to prompt recurrence of symptoms in a dose-independent manner. Other drugs may lead to pancreatitis by inducing known risk factors for acute pancreatitis. For instance, estrogens, ritonavir,  $\beta$ -blockers, and other drugs are known to induce hyperlipidemia in susceptible patients. Hypercalcemia may develop secondary to excessive vitamin D intake. Erythromycin, somatostatin, and codeine increase the pressure of the sphincter of Oddi and may thereby induce pancreatitis. ACE-inhibitors may possibly obstruct pancreatic ducts by localised angioedema. However, for most drugs the mechanism of acute pancreatitis remains speculative.

The incidence of drug-induced pancreatitis is unknown. Reports to adverse reaction monitoring centers seem to indicate a low incidence of drug-induced pancreatitis, but due to underreporting incidence rates cannot be validly estimated from spontaneous reports.(25,29,52) In clinical studies on acute pancreatitis, 1-2% is attributed to drugs,(2,583,584) with a peak of 6.5% in one study.(585) This would correspond to an incidence of drug-induced acute pancreatitis of approximately 2-4 per million inhabitants. However this might well be an underestimation as drugs are probably frequently overlooked as a possible cause of acute pancreatitis. The proportion of acute pancreatitis attributed to drugs is relatively high in children (15%),(4) probably because gallstones and alcohol abuse are rare in this age group. A study that compared patients with and without HIV infection found a drug-related aetiology in 41% and 5% of the patients with acute pancreatitis respectively.(34)

Drug-induced acute pancreatitis does not have unique features that distinguish it from acute pancreatitis due to other causes. Diagnosis and treatment of drug-induced pancreatitis relies on the same principles as diagnosis and treatment of acute pancreatitis to other causes. One study on the severity of drug-induced acute pancreatitis concluded that it usually runs a benign course.(583) Probably this is true as 75 to 80% of all episodes of acute pancreatitis runs a benign course. However, we are not aware of other studies demonstrating that the course in drug-induced acute pancreatitis is milder than in acute pancreatitis to other causes. Although the authors claimed that pancreatitis did not contribute to their death, 2 out of 22 (9%) patients with drug-induced pancreatitis died, a figure comparable to case-fatality rates in other studies. Indeed many reports on fatal acute pancreatitis attributed to drug treatment show that drug-induced pancreatitis may be a very severe clinical condition.

A wide variety of drugs have been suspected of causing pancreatitis. Relatively new drugs such as HIV protease inhibitors, losartan and interferon have recently been published as a potential cause of acute pancreatitis. 48 drugs have a definite or probable causal relationship to acute pancreatitis. Despite numerous case-reports on drug-induced acute pancreatitis, quantitative information on this subject is scanty.

Formal epidemiological studies are needed to quantify the risk of drug-induced acute pancreatitis.

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CHAPTER 4

*four*

*Drug-induced  
acute pancreatitis:  
analytical studies*



The risk of acute pancreatitis  
associated with acid-suppressing  
drugs

4.1

## **The risk of acute pancreatitis associated with acid-suppressing drugs**

**Introduction:** Several anti-ulcer drugs have been associated with acute pancreatitis in case reports. We quantified the risk of acute pancreatitis associated with use of acid-suppressing drugs.

**Methods:** We conducted a retrospective cohort study with a nested case-control design within the General Practice Research Database (GPRD) in the United Kingdom. The cohort included 180,178 persons aged 20 to 74 years, who had received at least one prescription of cimetidine, famotidine, nizatidine, ranitidine, lansoprazole, or omeprazole from January 1992 to September 1997 and who did not have major risk factors for pancreatic diseases. Patients with a computerized medical history compatible with idiopathic acute pancreatitis were validated through review of medical records. For the nested case-control analysis 1000 controls were randomly selected from the study population.

**Results:** We identified 88 potential cases of idiopathic acute pancreatitis. Medical records were available for 86. After review of these records 36 cases of acute pancreatitis were confirmed. Seven cases occurred during non-use, corresponding to a background incidence rate (IR) of 4.4/100,000 person-years (PY). Six cases occurred during current use of ranitidine (IR 10.5/100,000 PY), five patients were current users of cimetidine (IR 13.9/100,000 PY), and three were current users of omeprazole (IR 7.8/100,000 PY). There were no cases among current users of famotidine, lansoprazole, or nizatidine. Relative risk (RR) compared to non-use and corrected for age, gender, calendar year and use of medication formerly associated with acute pancreatitis was 1.3 (95% CI: 0.5-3.3) for ranitidine, 2.1 (95% CI: 0.6-7.2) for cimetidine, and 1.1 (95% CI: 0.4-4.6) for omeprazole.

**Conclusion:** The results of this study do not suggest a major increased risk of acute pancreatitis associated with use of acid-suppressing drugs.

## INTRODUCTION

Several drugs have been implicated as possible causes of acute pancreatitis.(1-3) Most information on drug-induced acute pancreatitis is derived from anecdotal case-reports, and very little is known about the incidence and mechanisms of drug-induced acute pancreatitis.

Cimetidine, famotidine, nizatidine, ranitidine, lansoprazole, and omeprazole are extensively used in the treatment of peptic ulcer disease, and reflux esophagitis. Adverse drug reactions concerning the central nervous system, the kidneys, the haematological system, the gastrointestinal tract, and the cardiovascular system have been attributed to these acid-suppressing drugs.(4) Cimetidine and ranitidine have been associated with acute pancreatitis in several case-reports.(5-9) Although a relationship was found between cimetidine and acute pancreatitis in rats,(10) others have questioned this.(11) A record-linkage case-control study showed a crude significant association between cimetidine, ranitidine and acute pancreatitis, but this association disappeared after adjustment for potential confounders.(12)

In view of the controversies regarding the association between acid-suppressing drugs and acute pancreatitis, we conducted a retrospective cohort study in the General Practice Research Database (GPRD) in the United Kingdom (UK) to assess the risk of acute pancreatitis associated with the use of cimetidine, famotidine, nizatidine, ranitidine, lansoprazole, and omeprazole. A nested case-control analysis was conducted to examine in more detail the relationship between dose and duration of treatment, and the risk of acute pancreatitis.

## METHODS

### Setting

Over 4 million residents in the UK are registered with general practitioners (GPs) who participate in the GPRD database. Medical data on these 4 million patients are continuously recorded and sent anonymously to the Office of National Statistics (ONS) in order to be used for research projects. The computerized information contains demographic data, general practitioner consultations, referrals to consultants and hospitals, and all prescriptions issued. Indications for new courses of treatment are routinely stored in the database. In addition, the GP may record laboratory test results and other medical data in a free text comment field. A modification of the Oxford Medical Information System (OXMIS) classification is used to code specific diagnoses. Previous validation studies have found that over 90% of all referrals are recorded with a code that reflects the specialist's diagnosis. (13,14) Drugs are coded according to a

drug dictionary based on data from the Prescription Pricing Authority.

### **Source population**

The source population consisted of all patients aged 20 to 74 years registered with 337 general practitioner practices with a permanent registration status during the study period January 1st 1992 and September 30th 1997.

### **Study Cohort**

The study cohort comprised all patients who received at least one prescription for cimetidine, famotidine, nizatidine, ranitidine, lansoprazole, or omeprazole during the study period. We excluded all subjects with a history of acute pancreatitis or assessment of amylase before the date of the first prescription of a study drug. Patients with a diagnosis of cancer, alcoholism, biliary- or pancreatic diseases, and biliary or pancreatic surgical procedures within five years before study entry were also removed from the cohort. The remaining patients were followed from the date of the first prescription of one of the study drugs to the earliest of the following events: development of acute pancreatitis, assessment of amylase, one of the above mentioned clinical exclusion criteria, death, or end of the study period.

### **Case ascertainment**

With a computerized search we identified all study members who had a code for acute pancreatitis or a code for assessment of amylase. Subsequently, the complete computerized patient profiles blinded to drug exposure were manually reviewed to exclude all patients who were not referred to a specialist or hospital, all patients with a diagnosis of cancer, alcoholism, cholelithiasis, postoperative pancreatitis, other pancreatic disorders, and all patients in whom the diagnosis of acute pancreatitis was clearly excluded. Potential cases were those for whom the information in the patient profiles was compatible with idiopathic acute pancreatitis.

### **Case validation**

We requested the medical records of all potential cases ( $n = 88$ ) from the GPs. Received records were, independently and blinded to exposure, validated by all four authors. Based on this information, we excluded all individuals who had any evidence of alcohol abuse, cholelithiasis, chronic pancreatitis, malignant neoplasms, any other well-defined condition associated with the development of acute pancreatitis, or if symptoms of acute pancreatitis started before start of follow-up. Consensus was

reached on all cases. The diagnosis was accepted when acute pancreatitis was explicitly mentioned in the discharge letter or when there was a clinical picture compatible with acute pancreatitis together with one of the following criteria: an increase in serum amylase or lipase of  $>2$  times the upper limit of normal, confirmatory evidence of acute pancreatitis at imaging procedures or at laparotomy or autopsy.

### **Cohort analysis**

Person-time contributed by the study participants was divided into three mutually exclusive categories: current use, past use and non-use. Current use was defined as the person time experienced during the length of an acid-suppressing drug prescription and six days thereafter. Past use included the period up to 365 days after the end of current use. Consequently, the time window of non-use started at the end of past use. Incidence rates were calculated by dividing the total number of cases of acute pancreatitis by the corresponding total amount of person-time experienced. Ninety-five percent confidence intervals (95% CIs) were calculated based on a Poisson distribution.

Adjusted estimates of relative risks and 95% CIs associated with current and past use as compared to non-use were computed using a Poisson regression model with age, sex, and calendar year included in the model.

### **Nested case-control analysis**

In order to explore dose and duration effects we performed a nested case-control analysis within the study cohort. All confirmed cases were used in the nested case-control analysis. The index date for the cases was the date of start of symptoms compatible with acute pancreatitis (same index date as used in the cohort analysis). In order to ascertain controls, a random date during the study period was generated for all study participants. A subject was an eligible control when the random date was included in his or her follow-up time. All exclusion criteria applied to the selection of the cases were also applied to the controls. From the list of eligible controls, we randomly selected 1000 controls and their random date was defined as the index date.

A participant was defined as a current user of one of the study drugs if the index date fell within the prescription period or when the end date of the last prescription fell within six days preceding the index date. A person was defined as a past user when the end date of the last consecutive prescription period fell within seven to 371 days before the index date. A person was defined as a non-user when none of the study drugs were used in the 371 days preceding the index date. Estimates of the odds ratios and their 95% CIs were calculated with logistic regression analyses comparing current and past use with non-use of the individual acid-suppressing drugs. Age, sex, calendar

year, and presence of other drugs associated with acute pancreatitis(3) (ACE-inhibitors, aminosalicylates, NSAIDs, estrogens, furosemide, thiazide diuretics, valproic acid, and azathioprine) were included in the model to control for potential confounding.

## RESULTS

The study cohort consisted of 180,178 subjects who received at least one prescription of cimetidine, famotidine, nizatidine, ranitidine, lansoprazole, or omeprazole. Overall 1,545,921 prescriptions of these acid-suppressing drugs were written during the study period. The age and gender distribution of users of individual acid-suppressing drugs is presented in table 1. There were 88 patients who had a computerized history compatible with an idiopathic episode of acute pancreatitis and for whom medical records were requested from the GPs. Of two patients, no information was received. Of the remaining 86 patients, 36 (42%) were classified as cases. The remainder was excluded because of alcohol abuse (n = 11), cholelithiasis (n = 10), and cancer, other pancreatic disorders and postoperative pancreatitis in 11 patients. The diagnosis of acute pancreatitis was not confirmed in 11 patients. In the remaining 7 patients onset of symptoms was before start of follow-up.

The overall incidence rate of idiopathic acute pancreatitis during current use of acid-suppressing drugs was 9.9 (95% CI: 4.7-15.1) per 100,000 person years (PY), 7.6 (95% CI: 3.8-11.5) per 100,000 PY for past users, and 4.4 (95% CI: 1.1-7.6) per 100,000 PY for non-users. After adjustment for age, gender and calendar year the RR was 1.6 (95% CI: 0.6-4.2) for current use and 1.6 (95% CI: 0.6-4.0) for past use of an acid-suppressing drug. Incidence rates and RRs for individual acid-suppressing drugs are given in table 2.

Table 3 shows the results of the nested case-control analysis. Out of the 36 cases, 20 (56%) were male and the mean age was 61 years. Use of acid-suppressing drugs,

**Table 1**  
Age and gender distribution

	Total*	Male	Female	20-59y	60-74y
Overall	1,545,921	52%	48%	51%	49%
Cimetidine	382,767	52%	48%	51%	49%
Famotidine	16,797	52%	48%	50%	50%
Lansoprazole	54,554	51%	49%	57%	43%
Nizatidine	49,079	51%	49%	51%	49%
Omeprazole	439,104	50%	50%	51%	49%
Ranitidine	603,62	53%	47%	49%	51%

\* Number of prescriptions

**Table 2**

Incidence rates of and relative risks of acute pancreatitis for individual acid-suppressing drugs

	Person-years	cases	IR/10 <sup>5</sup>	Crude RR (95% CI)	RR (95% CI)*
Non-users†	160430	7	4.4		
Current-use‡	141738	14	9.9	2.3 (0.9-5.6)	1.6 (0.6-4.2)
cimetidine	35966	5	13.9	3.2 (1.0-10.0)	2.3 (0.7-7.7)
famotidine	1551	0	-		
lansoprazole	4567	0	-		
nizatidine	4262	0	-		
omeprazole	38430	3	7.8	1.8 (0.5-6.9)	1.3 (0.3-5.3)
ranitidine	56961	6	10.5	2.4 (0.8-7.2)	1.7 (0.6-5.4)
Past use§	196356	15	7.6	1.8 (0.7-4.3)	1.6 (0.6-4.0)

\* Age, gender and calendar year were included in the Poisson regression model

† No use of an acid-suppressing drug in the 371 days preceding the index date.

‡ Use of an acid-suppressing drug on the index date or the 6 days preceding the index date.

§ Use of an acid-suppressing drug in days 7-371 before the index date.

**Table 3**

Relative risk of acute pancreatitis associated with use of acid-suppressing drugs and other factors

	Cases (n=36)	Controls (n=1000)	OR (95% CI)
Acid-suppressing drug			
Non-use†	7	306	
Current use‡	14	281	1.4 (0.5-3.6)
Cimetidine	5	65	2.1 (0.6-7.2)*
Omeprazole	3	69	1.1 (0.3-4.6)*
Ranitidine	6	129	1.3 (0.4-4.1)*
Past users§	15	431	1.3 (0.5-3.3)*
Age			
20-59 years	12	639	
60-74 years	24	361	3.1 (1.5-6.4)
Gender			
Male	20	486	
Female	16	514	0.6 (0.3-1.2)
Year category			
1992-1994	16	400	
1995-1997	20	600	0.9 (0.5-1.8)
Pancreatotoxic medication			
Non-use	21	760	
Current use	15	240	2.0 (1.0-4.2)

\* Adjusted for age, gender, calendar year, and current use of other pancreatotoxic medication.

† No use of an acid-suppressing drug in the 371 days preceding the index date.

‡ Use of an acid-suppressing drug on the index date or within the 6 days preceding the index date.

§ Use of an acid-suppressing drug in days 7-371 before the index date.

|| End of study in September 1997

**Table 4**

Influence of duration of acid-suppressing drug therapy on the risk of acute pancreatitis

	Cases (n = 36)	Controls (n = 1000)	OR (95% CI) *
Duration of anti-ulcer therapy†			
≤ 30 days	3	47	2.3 (0.5-9.5)
> 30 days	11	234	1.1 (0.4-3.3)
Daily dose of cimetidine†, ‡			
< 800 mg	2	22	2.2 (0.4-12.6)
≥ 800 mg	3	41	1.7 (0.4-7.7)
Daily dose of ranitidine†, §			
< 300 mg	2	26	1.9 (0.3-10.3)
≥ 300 mg	4	100	1.1 (0.3-4.2)

\* Adjusted for age, gender, calendar year, and current use of other pancreatotoxic medication.

† Current use compared to non-use

‡ Data on daily dose of cimetidine was not available for 2 controls

§ Data on daily dose of ranitidine was not available for 3 controls

gender and calendar year were not significantly associated with acute pancreatitis. The RR among current users of medications suspected to be associated with acute pancreatitis was 2.0 (95% CI: 1.0-4.2). Age was the only factor that was significantly associated with the occurrence of acute pancreatitis. Although not significant, the risk of acute pancreatitis was higher in the first month of acid-suppressing therapy: 2.3 (95% CI: 0.5-9.5) versus 1.1 (95% CI: 0.4-3.3) for long-term users. Exclusion of all current users of medications formerly associated with acute pancreatitis did not change the risk estimates considerably (data not shown). A dose-response relationship was not observed in users of cimetidine or ranitidine (table 4).

## DISCUSSION

In this large cohort study, we observed no major increased risk of acute pancreatitis in users of acid-suppressing drugs. Cimetidine was the only acid-suppressing drug with a small increased risk of acute pancreatitis, but this association was no longer present after adjustment for potential confounders. There was a tendency towards an increased risk in the first month of treatment. The daily dosage of acid-suppressing drugs had no effect on the risk of acute pancreatitis.

The validity of epidemiological studies may suffer from selection bias, information bias or confounding. The presence of selection bias in this study is unlikely as identification of the study population was based on prerecorded prescriptions of acid-suppressing drugs, and therefore unrelated to the outcome of interest. Since drug exposure was recorded before the onset of disease, recall bias is not present. Case

histories concerning the relationship between H2-blockers and acute pancreatitis have been published since the late seventies, some of them proven by recurrence of symptoms after restart of treatment.(6,9) Physicians may therefore diagnose acute pancreatitis more easily in patients using these H2-receptor blockers. This diagnostic bias might therefore explain the non-significant increase in RR of cimetidine and ranitidine seen in this study. Patients with gastric acid related diseases will pay more visits to gastroenterological consultants and may therefore have acute pancreatitis more easily detected. However, as none of the acute pancreatitis diagnoses was made during routine check-ups of anti-ulcer treatment we expect diagnostic bias to play a minor role if any in explaining the results. Misclassification of outcome was limited due to review of the medical records of potential cases. Misclassification of exposure, for instance by non-compliance or dispensing of acid-suppressing drugs in hospital was probably non-differential and would therefore have biased the risk estimates towards null.

By restricting the study to people without major risk factors for acute pancreatitis we tried to control for confounding by these factors.

A recent study on the association between H2-receptor antagonists and acute pancreatitis reported a non-significant RR of 3.7 for cimetidine and a non-significant RR of 3.1 for ranitidine.(12) In patients without risk factors for acute pancreatitis these figures were 2.0 and 2.5 respectively. The authors concluded that the higher RRs might be due to residual confounding. Prescribing of acid-suppressing drugs for prodromal symptoms of acute pancreatitis, sometimes referred to as protopathic bias could be an alternative explanation for the small increased risk seen in the former study and in our study. We tried to reduce the play of protopathic bias by taking the day of onset symptoms as index date for patients with acute pancreatitis. The risk in the first 30 days of therapy was somewhat higher than the risk thereafter, albeit non-significantly. This could indicate either an acute effect or imperfect control of protopathic bias. However, protopathic bias cannot explain the different risk estimates for the different acid-suppressing drugs as this form of selection bias would affect all acid-suppressing drugs alike.

In conclusion, the results of this study do not suggest a major increased risk for acute pancreatitis associated with the use of acid-suppressing drugs.

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The risk of acute pancreatitis  
associated with angiotensin-  
converting enzyme inhibitors

4.2

## **Angiotensin-converting enzyme inhibitors increase the risk of acute pancreatitis: The European case-control study on drug-induced acute pancreatitis (EDIP)**

***Introduction:** Angiotensin-converting enzyme (ACE) inhibitors have been associated with acute pancreatitis in several case-reports. We quantified the risk of acute pancreatitis associated with the use of ACE-inhibitors in the European study on drug-induced acute pancreatitis (EDIP).*

***Methods:** The EDIP study is a multi-centre population-based European case-control study on the association between drug use and acute pancreatitis. Patients between 40 and 85 years of age with acute pancreatitis were included between October 1st 1994 and December 31st 1998. For each case, age- and gender-matched community controls were recruited. Detailed information on drug use and potential confounders (e.g. co-morbidity, alcohol use) was obtained through a structured interview.*

***Results:** During the study period, we identified and interviewed 724 patients with acute pancreatitis and 1791 community controls. A high number of previous hospitalisations, smoking, high intake of alcohol, a history of biliary disease, hyperlipidemia, peptic ulcer disease, pancreatic disease, ischemic heart disease, hypertension, and congestive heart failure were positively associated with development of acute pancreatitis. Relative to non-use, use of ACE-inhibitors in the week prior to the index date increased the risk of acute pancreatitis by 60% (95% CI: 1.1-2.3). The risk of acute pancreatitis associated with ACE-inhibitor use increased with higher daily doses and was most pronounced in patients who did not have biliary diseases; relative risk 2.7 (95% CI: 1.3-5.8)*

***Interpretation:** Use of ACE-inhibitors is associated with a modest increase in risk of acute pancreatitis, but this risk seems substantially higher in patients without biliary diseases.*

## INTRODUCTION

Acute pancreatitis is an inflammatory disease of the pancreas which may lead to considerable morbidity and mortality. The incidence of acute pancreatitis shows an increasing trend in European countries.(1,2) The most important risk factors for acute pancreatitis are gallstones and alcohol abuse. Other risk factors include hyperlipidemia, hypercalcemia, and endoscopic retrograde cholangiopancreatography (ERCP). The etiology remains unknown in 10 to 25% of patients with acute pancreatitis.(3)

Drugs have since long been implicated as a potential cause of acute pancreatitis.(4) Most information on drug-induced acute pancreatitis is derived from anecdotal case-reports and little is known about the incidence and mechanisms of drug-induced acute pancreatitis.(5)

Angiotensin-converting enzyme (ACE) inhibitors are extensively used in the treatment of hypertension, congestive heart failure, and diabetic nephropathy.(6) Acute pancreatitis attributed to ACE-inhibitors has been described in case-reports,(7-26) some with recurrence of pancreatitis after rechallenge. (7-9) However, quantitative information on the association between ACE-inhibitors and acute pancreatitis is not available. Therefore, we studied the risk of acute pancreatitis associated with use of ACE-inhibitors in the European study on drug-induced acute pancreatitis (EDIP).

## METHODS

### Setting

This study is part of the European case-control study on drug-induced acute pancreatitis (EDIP) which was initiated by the European Pharmacovigilance Research Group. Participating countries include Denmark, Italy, the Netherlands, Portugal, Sweden, and the United Kingdom. The source population comprised all persons between 40 to 85 years of age in the county of Funen in Denmark, the Rijnmond area in the Netherlands, the Coimbra area in Portugal, the cities Malmö, Stockholm, Uppsala, and Umeå in Sweden, the cities Bologna, Bolzano, Milano, and Verona in Italy, and Birmingham city in the United Kingdom. For the present study only data from Denmark, the Netherlands, Italy, and Sweden was used because of absence of data on community controls in the other countries. The study period ran from October 1st 1994 to December 31st 1998, but differed in the participating countries. Local medical ethical committees approved the study, and written informed consent was obtained from all participants.

## Case identification and validation

In the Netherlands, Sweden, and Denmark potential cases were identified by regular screening of serum amylase and lipase values of admitted patients in the participating hospitals. In Italy, the departments of internal medicine, gastroenterology, and surgery were regularly screened for patients admitted with acute abdominal pain. Patients were considered potential cases of acute pancreatitis if they had acute abdominal pain combined with elevated serum amylase and lipase values of more than 2 times the upper limit of normal within the first week of admission, or if they had acute abdominal pain with confirmatory evidence of acute pancreatitis on ultrasonography, computerized tomography, laparotomy, or autopsy. Patients with post-ERCP pancreatitis, abdominal trauma, a perforated gastrointestinal ulcer, malignancy of the gastrointestinal tract, a positive HIV test, or chronic pancreatitis were excluded. Additionally, patients were excluded if they were resident in a nursing home, did not speak the native language, died before study assessments were completed, or if no reliable interview data could be obtained (e.g. due to dementia). Since Sweden combined the EDIP study with a national study, their exclusion criteria were slightly different in the cities Stockholm and Umeå. In these cities, patients with a history of biliary diseases and patients with a relapse of acute pancreatitis were excluded. Acute pancreatitis was considered of biliary origin if gallstones were present at imaging procedures or at laparotomy.

The clinical notes of all eligible cases were reviewed by consultant gastroenterologists who were blinded to drug exposure. The index date for the cases was defined as the date of first recorded symptoms.

## Control selection

In Sweden, Denmark, and Italy community controls were randomly selected from population registries. Community controls were randomly selected from the general practitioner's practice of the case in the Netherlands. Controls were matched to cases on gender and age ( $\pm 5$  years). The index date of the controls was defined as the date of interview. Exclusion criteria for controls were equal to exclusion criteria for cases.

## Data collection

Each country used similar structured questionnaires and coding manuals (International Classification of Diseases, 9th edition and the Drug Dictionary of the World Health Organization). Interviewers were centrally trained and supervised. The questionnaire included questions on demographics, life-long medical history, smoking and drinking habits, plus drug intake in the preceding six months. In order to reduce

recall bias, participants were asked to retrieve all packages of drugs that they had used before start of the interview. For each drug, the indication, strength, formulation, dosing regimen, start and stop dates were recorded.

## **Exposure**

Use of ACE-inhibitors was defined as use of benazepril, captopril, cilazapril, enalapril, fosinopril, lisinopril, perindopril, quinapril, or ramipril within one week before the index date. The dose of ACE inhibitor use was expressed in defined daily dosages (DDD), in which one DDD was the recommended dose for the main indication in adults.<sup>(27)</sup> For ACE-inhibitors the values corresponding to one DDD are: benazepril 7.5 mg, captopril 50 mg, cilazapril 2.5 mg, enalapril 10 mg, fosinopril 15 mg, lisinopril 10 mg, perindopril 4 mg, quinapril 15 mg, and ramipril 2.5 mg. The daily dosage of ACE-inhibitors was classified as low (< 1DDD), moderate (1-2 DDD), and high (>2 DDD). To study potential recall bias, we verified ACE-inhibitor use at the community pharmacy of the participants in the Netherlands.

## **Covariates**

As potential confounders we considered smoking, alcohol use, and co-morbidity. Smoking was expressed as the number of cigarettes smoked per day: 0, 1-10, 11-20, and more than 21. Alcohol use was expressed as the average intake of per day: 1 unit, 2-4 units, 5-7 units, and 8 or more units. Weight categories were created on the basis of body mass index (BMI): underweight (<18.5), normal ( $\geq 18.5 - < 25$ ), overweight ( $\geq 25 - < 30$ ), and obese ( $\geq 30$ ).<sup>(28)</sup> Working status was divided into employed, ill, unemployed, student or military service, and other.

## **Analyses**

Maximum likelihood estimates of odds ratios (ORs) and their 95% confidence intervals (CIs) were computed using a conditional logistic regression model. In the multivariate analysis risk estimates for use of ACE-inhibitors were adjusted for alcohol use, smoking, BMI, history of pancreatic disease, history of biliary disease, history of diabetes mellitus, history of hypertension, heart failure, and use of other antihypertensive medication (angiotensin II receptor blockers, calcium channel blockers,  $\beta$ -blockers, diuretics). We performed additional analyses restricted to patients with a first attack of acute pancreatitis and patients with non-biliary acute pancreatitis. All analyses were performed in SPSS 8.0 for Windows.

**Table 1**  
Patient characteristics

		Cases (n = 724)	Community controls (n = 1791)	OR <sub>unadjusted</sub>
Country	Denmark	69	155	
	Italy	120	151	
	Netherlands	112	112	
	Sweden	423	1373	
Male		422	930	
Age (years)		62.7 (SD 11.7)	60.6 (SD 11.9)	
BMI		25.7 (SD 4.1)	25.2 (SD 3.7)	
	< 18.5	10	25	1.2 (0.6-2.7)
	≥ 18.5 - < 25	328	895	ref.
	≥ 25 - < 30	288	663	1.1 (0.9-1.4)
	≥ 30	90	185	1.3 (0.9-1.7)
	Unknown	8	23	
No. Hosp.*	0	78	250	ref.
	1	148	387	1.3 (0.9-1.8)
	2	139	337	1.3 (0.9-1.8)
	3	97	270	1.2 (0.8-1.7)
	4	80	195	1.4 (0.9-2.0)
	≥ 5	181	349	1.7 (1.3-2.4)
	Unknown	1	3	
Smoking†	0	509	1343	ref.
	1-10	67	197	0.9 (0.7-1.3)
	11-20	116	196	1.7 (1.3-2.2)
	≥ 21	29	37	2.0 (1.1-3.4)
	Unknown	3	18	
Alcohol use‡	0	152	276	1.3 (0.97-1.6)
	1-7	321	927	ref.
	8-28	181	526	0.8 (0.7-1.1)
	29-49	24	43	1.2 (0.7-2.1)
	≥ 50	40	6	15.3 (5.9-39.9)
	Unknown	6	13	
ADR§		199	539	1.1 (0.9-1.3)
Knowledge on ADR¶		33	196	0.4 (0.3-0.6)
Gall tract diseases	≤ 1 yr.	34	8	11.7 (5.3-25.8)
	2-5 yr.	18	12	3.5 (1.6-7.8)
	> 5 yr.	75	179	1.2 (0.9-1.6)
Hyperlipidemia§		49	70	1.7 (1.2-2.5)
Ulcer pepticum§		92	114	2.0 (1.5-2.8)
Renal failure§		8	9	1.9 (0.7-5.2)
Inflammatory bowel disease§		9	14	2.2 (0.9-5.1)
Pancreas diseases§		52	9	13.8 (6.4-29.2)
Hypertension§		229	432	1.3 (1.1-1.6)
Ischemic heart disease§		98	136	1.8 (1.4-2.4)
Congestive heart failure§		21	21	2.3 (1.2-4.3)
Diabetes mellitus§		70	77	2.1 (1.5-3.0)
Vitamin C**		44	130	0.9 (0.6-1.3)

OR=odds ratio, SD=standard deviation, BMI=body mass index, ADR=adverse drug reaction, \* Number of hospitalisations in entire life, † number of cigarettes smoker per day, ‡ Units of alcohol per week, § Ever history of, ¶ Knowledge that drugs may cause acute pancreatitis, \*\* use in the week before the index date.

## RESULTS

During the study period 823 cases met our inclusion criteria. After the expert review, 80 cases were excluded as the diagnosis acute pancreatitis could not be substantiated. Furthermore, 19 cases did not have a matched community control and were therefore excluded from the analyses. Among the final 724 cases, 658 (91%) were admitted for a first attack of acute pancreatitis. Three hundred (41%) patients had evidence of gallstones and 88 (12%) patients had a history of alcohol abuse or used 5 units of alcohol or more per day. A total of 1791 community controls were matched to the final 724 cases. Data on dispensed prescriptions of ACE-inhibitors at community pharmacies showed that data on ACE-inhibitor use was complete in the Netherlands.

A high number of hospitalisations, smoking, high intake of alcohol, and a history of biliary disease, hyperlipidemia, peptic ulcer disease, pancreatic disease, diabetes mellitus, ischemic heart disease, and congestive heart failure were all positively associated with development of acute pancreatitis (table 1).

A higher proportion of patients with acute pancreatitis reported use of ACE-inhibitors than controls (table 2). Use of an ACE-inhibitor increased the risk of acute pancreatitis by 60% (95% CI; 1.1-2.3). Although the relative risk estimates varied slightly between individual ACE inhibitors, the confidence intervals overlapped. Additional adjustment for year of ascertainment had no considerable effect on the risk estimate. The risk of acute pancreatitis was higher during the first 6 months of therapy than during prolonged use (table 2). We observed a positive dose-effect relationship between daily dose of ACE inhibitors and acute pancreatitis (table 2). The risk of acute pancreatitis associated with the use of ACE-inhibitors was higher in patients without biliary diseases: 2.7 (95% CI: 1.3-5.8). Restriction of the analyses to patients with a

**Table 2**  
Association between use of ACE-inhibitors and acute pancreatitis

	Cases (n = 724)	Community controls (n = 1791)	OR <sub>adjusted</sub> †
ACE-inhibitors*	83	117	1.6 (1.1-2.3)
Daily dose			
< 1DDD	20	34	1.2 (0.6-2.3)
1-2 DDD	55	77	1.8 (1.1-2.8)
> 2 DDD	7	4	3.5 (0.8-14.9)
Unknown	1	2	
Duration of use			
≤ 6 months	17	15	3.3 (1.4-7.6)
> 6 months	66	102	1.4 (0.9-2.1)

ACE-inhibitor = angiotensin-converting enzyme inhibitor, DDD = defined daily dosage, \*use in the week before the index date, † adjusted for other antihypertensive medication, alcohol use, smoking, bmi, history of pancreatic disease, history of biliary disease, history of diabetes mellitus, history of hypertension, history of heart failure.

**Table 3**

Association between use of other antihypertensive medication and acute pancreatitis

Antihypertensive medication *	Cases (n = 724)	Community controls (n = 1791)	OR <sub>adjusted</sub> †
AT-II-blockers	8	22	0.9 (0.4-2.1)
CCB	95	141	1.5 (1.1-2.2)
K <sup>+</sup> -sparing diuretics	41	70	1.7 (1.0-2.9)
Loop diuretics	47	94	0.6 (0.4-0.95)
Thiazide diuretics	44	91	0.7 (0.4-1.2)
β-blockers	96	183	1.3 (0.96-1.8)

AT-II=angiotensine II receptor blockers, CCB=calcium channel blockers, K<sup>+</sup> = potassium, \*use in the week before the index date, † adjusted for other antihypertensive medication, alcohol use, smoking, bmi, history of pancreatic, history of biliary disease, history of diabetes mellitus, history of hypertension, history of heart failure.

first attack of acute pancreatitis did not change the results considerably. Among the antihypertensive drugs, use of calcium channel blockers and use of potassium sparing diuretics was also significantly associated with acute pancreatitis. Concomitant use of other antihypertensive medication did not increase the risk of acute pancreatitis significantly (table 3).

## DISCUSSION

In this multinational study we demonstrated that use of ACE-inhibitors increased the risk of acute pancreatitis by approximately 60%. The risk of acute pancreatitis was highest among new users of ACE-inhibitors and at higher daily dosages. The risk of acute pancreatitis rose considerably when the analyses were restricted to patients without biliary disease, probably because the background rate of acute pancreatitis in this subpopulation is much lower.

ACE-inhibitors have been associated with acute pancreatitis since 1988. Over the years, enalapril, lisinopril, captopril, perindopril, quinapril, and benazepril have all been incriminated as a potential cause of acute pancreatitis.(7-26) Time between start of therapy with ACE-inhibitors and development of symptoms varied greatly in these case-reports from almost immediately to two years. Three patients experienced a relapse after restart of captopril, enalapril, and perindopril respectively.(7-9) Interestingly, one patient with losartan-associated acute pancreatitis had experienced an earlier episode of acute pancreatitis 5 days after starting enalapril treatment.(29) To our knowledge the association between ACE-inhibitors and pancreatitis has not been studied before in epidemiological studies.

As with all other causes of acute pancreatitis, the mechanism by which ACE-inhibi-

tors cause acute pancreatitis remains speculative. Pancreatic duct obstruction by local angioedema has been proposed as a possible mechanism.(12) Others argue that ACE-inhibitors may have a direct toxic effect on pancreatic cells as ACE-inhibitors can induce hypoglycemia.(22) Because captopril is structurally dissimilar to enalapril and lisinopril, an allergic reaction seems less likely. Apart from converting angiotensin I to angiotensin II, ACE also degrades both bradykinin and substance P.(30) Although probably not involved in the initiation of acute pancreatitis, kinins are involved in the formation of pancreatic edema. (31) In experimental models, kinin B2 receptor antagonists reduce edema formation in the pancreas.(31) Substance P is released from nerve endings and acts via NK1 receptors. Pancreatic substance P levels and NK1 receptors are upregulated during acute pancreatitis.(32) Knockout mice deficient in NK1 receptors are protected against pancreatitis. In contrast, knockout mice deficient in an enzyme that hydrolyses substance P are more susceptible to experimental acute pancreatitis.(32) Increased pancreatic kinin and substance P levels may therefore contribute to the development of acute pancreatitis.

Apart from ACE-inhibitors, calcium channel blockers were associated with an elevated risk of acute pancreatitis. To our knowledge acute pancreatitis attributed to calcium channel blockers is only mentioned in a survey from a spontaneous reporting center.(33) Recent evidence showed that elevated intracellular calcium levels are important in the premature activation of trypsinogen.(34) This would plea against an association between calcium channel blockers and acute pancreatitis. Indeed one experimental study in animals found a protective effect of verapamil on the development of caerulein-induced acute pancreatitis.(35) We could not substantiate earlier findings on loop and thiazide diuretic-associated acute pancreatitis.(36,37) However, these early studies on drug-induced acute pancreatitis did not control for important confounding factors such as alcohol abuse.

A potential limitation of observational studies is their vulnerability to selection bias, information bias, and confounding. Selective case inclusion is unlikely because of the standardized and objective screening criteria and the population-based character of the study. Although mild cases may have been missed, symptomatic cases of acute pancreatitis are mostly recognized and admitted irrespective of the suspected etiology, hence selection bias is unlikely. Diagnostic bias due to diagnosing acute pancreatitis more easily in patients who use ACE-inhibitors is not likely due to the acute nature of the disease, the screening procedures that we used, and due to the widespread belief that drugs have a low attributable risk for acute pancreatitis. In addition, all cases were validated by experts who were blinded to exposure.

Information bias regarding exposure is a particular problem in case-control studies as cases might recall drug use more accurately than controls due to their recent illness. However, verification at community pharmacies in the Netherland showed that data on ACE-inhibitor use was complete for cases and controls. In addition, we studied

the influence of recall bias by including a question on use of vitamin C (not known to be associated with acute pancreatitis) and by asking whether participants knew that drugs may cause acute pancreatitis. Vitamin C was not associated with development of acute pancreatitis and slightly more controls than cases knew that drugs may be a possible cause of acute pancreatitis. These findings suggest that recall bias did not play a major role in our study.

In pharmaco-epidemiological studies, confounding by indication may be a potential problem. We adjusted for the major indications of ACE-inhibitors, namely diabetes mellitus, hypertension, and heart failure. In addition, angiotensine II receptor blockers are prescribed for similar indications, but they appeared not to be associated with an elevated risk of acute pancreatitis.

All our analyses were adjusted for smoking, alcohol abuse, body mass index, a history of biliary diseases, a history of diabetes, a history of pancreatic diseases, and use of other antihypertensive medication. We had no information on the presence of gallstones in controls at the time of interview. Therefore we adjusted for a history of biliary diseases which was strongly associated with an increased risk of acute pancreatitis.

In conclusion, ACE-inhibitors are associated with a small but significantly increased risk of acute pancreatitis. ACE-inhibitors should be considered as a possible cause in patients with acute pancreatitis.

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The risk of acute pancreatitis  
associated with psychotropic drugs

4.3

**The risk of acute pancreatitis associated with psychotropic drugs:  
The European case-control study on drug-induced acute pancreatitis (EDIP)**

*Introduction:* Antidepressant drugs and antipsychotic agents have been associated with acute pancreatitis in several case-reports. We quantified the risk of acute pancreatitis associated with the use of psychotropic medication in the European study on drug-induced acute pancreatitis (EDIP)

*Methods:* The EDIP study is a multi-centre population-based European case-control study on the association between drug use and acute pancreatitis. Patients between 40 and 85 years of age with acute pancreatitis were included between October 1st 1994 and December 31st 1998. For each case, age- and gender-matched community controls were recruited. Detailed information on drug use and potential confounders (e.g. co-morbidity, alcohol use) was obtained through a structured interview.

*Results:* During the study period, we identified and interviewed 724 patients with acute pancreatitis and 1791 community controls. A high number of previous hospitalisations, smoking, high intake of alcohol, a history of biliary disease, hyperlipidemia, peptic ulcer disease, and pancreatic disease were positively associated with development of acute pancreatitis. Use of TCAs, SSRIs, and benzodiazepines was not associated with an increased risk of acute pancreatitis. However, use of antipsychotic drugs in the week before the index date increased the risk of acute pancreatitis three fold (95% CI: 1.5-6.0). The risk of acute pancreatitis associated with antipsychotics was largely confined to patients aged 60 years and over: OR 4.1 (1.7-9.9).

*Conclusion:* Use of antipsychotic agents is associated with an increased risk of acute pancreatitis.

## INTRODUCTION

Acute pancreatitis is an inflammatory disease of the pancreas which may lead to considerable morbidity and mortality. The incidence of acute pancreatitis shows an increasing trend in European countries.(1,2) The most important risk factors for acute pancreatitis are gallstones and alcohol abuse. Other risk factors include hyperlipidemia, hypercalcemia, and endoscopic retrograde cholangiopancreatography (ERCP). The aetiology remains unknown in 10 to 25% of patients with acute pancreatitis.(3)

Drugs have since long been implicated as a potential cause of acute pancreatitis.(4) Most information on drug-induced acute pancreatitis is derived from anecdotal case-reports and little is known about the incidence and mechanisms of drug-induced acute pancreatitis.(5) Acute pancreatitis attributed to benzodiazepines has not been described, but acute pancreatitis has been associated with tricyclic antidepressants (TCA), (6-10) selective serotonin reuptake inhibitors (SSRI),(11) and antipsychotic agents (12-21) in several case-reports. Associations between psychotropic drug use and acute pancreatitis have not been studied in large populations. We studied the risk of acute pancreatitis associated with use of TCAs, SSRIs, benzodiazepines, and antipsychotics in the European study on drug-induced acute pancreatitis (EDIP).

## METHODS

### Setting

This study is part of the European case-control study on drug-induced acute pancreatitis (EDIP) which was initiated by the European Pharmacovigilance Research Group. Participating countries include Denmark, Italy, the Netherlands, Portugal, Sweden, and the United Kingdom. The source population comprised all persons 40 to 85 years of age in the county of Funen in Denmark, the Rijnmond area in the Netherlands, the Coimbra area in Portugal, the cities Malmö, Stockholm, Uppsala, and Umeå in Sweden, the cities Bologna, Bolzano, Milano, and Verona in Italy, and Birmingham city in the United Kingdom. For the present study only data from Denmark, the Netherlands, Italy, and Sweden was used because of absence of data on community controls in the other countries. The total study period ran from October 1st 1994 to December 31st 1998, but differed in the participating countries. Local medical ethical committees approved the study, and written informed consent was obtained from all participants.

## Case identification and validation

In the Netherlands, Sweden, and Denmark potential cases were identified by regular screening of serum amylase and lipase values of admitted patients in the participating hospitals. In Italy, the departments of internal medicine, gastroenterology, and surgery were regularly screened for patients admitted with acute abdominal pain. Patients were considered potential cases of acute pancreatitis if they had acute abdominal pain combined with elevated serum amylase and lipase values of more than 2 times the upper limit of normal within the first week of admission, or if they had acute abdominal pain with confirmatory evidence of acute pancreatitis on ultrasonography, computerised tomography, laparotomy, or autopsy. Patients with post-ERCP pancreatitis, abdominal trauma, a perforated gastrointestinal ulcer, malignancy of the gastrointestinal tract, a positive HIV test, or chronic pancreatitis were excluded. Additionally, patients were excluded if they were resident in a nursing home, did not speak the native language, died before the interview was conducted, or if no reliable drug history could be obtained. Since Sweden combined the EDIP study with a national study their exclusion criteria were slightly different in the cities Stockholm and Umeå. In these cities, patients with a history of biliary diseases and patients with a relapse of acute pancreatitis were also excluded. Acute pancreatitis was considered of biliary origin if gallstones were present at imaging procedures or at laparotomy.

The clinical notes of all eligible cases were reviewed by consultant gastroenterologists who were blinded to drug exposure. The index date for the cases was defined as the date of first recorded symptoms.

## Control selection

In Sweden, Denmark, and Italy community controls were randomly selected from population registries. Community controls were randomly selected from the general practitioner's practice of the case in the Netherlands. Controls were matched to cases on gender and age ( $\pm 5$  years). The index date of the controls was defined as the date of interview. Exclusion criteria for controls were equal to exclusion criteria for cases.

## Data collection

Each country used similar structured questionnaire and coding manuals (International Classification of Diseases, 9th edition and the Drug Dictionary of the World Health Organization). Interviewers were centrally trained and supervised. The questionnaire included questions on demographics, life-long medical history, smoking and drinking habits, plus drug intake in the preceding six months. In order to reduce recall bias, participants were asked to retrieve all packages of drugs that they had

used before start of the interview. For each drug, the indication, strength, formulation, dosing regimen, plus start and end of therapy were recorded.

## **Exposure**

Use of TCAs, SSRIs, benzodiazepines, or antipsychotic drugs was defined as use within one week before the index date. To study potential recall bias, we verified use of psychotropic drugs at the community pharmacy of the participants in the Netherlands.

## **Covariates**

As potential confounders we considered smoking, alcohol use, and co-morbidity. Smoking was expressed as the number of cigarettes smoked per day: 0, 1-10, 11-20, and more than 21. Alcohol use was expressed as the average intake of per day: 1 unit, 2-4 units, 5-7 units, and 8 or more units. Weight categories were created on the basis of body mass index (BMI): underweight ( $<18.5$ ), normal ( $\geq 18.5 - <25$ ), overweight ( $\geq 25 - <30$ ), and obese ( $\geq 30$ ).<sup>(22)</sup> Working status was divided into employed, ill, unemployed, student or military service, and other.

## **Analyses**

Maximum likelihood estimates of odds ratios (ORs) and their 95% confidence intervals (CIs) were computed using a conditional logistic regression model. In the multivariate analysis risk estimates for use of psychotropic drugs were adjusted for alcohol use, smoking, history of pancreatic disease, history of biliary disease, and history of diabetes mellitus. We performed additional analyses restricted to patients with a first attack of acute pancreatitis and patients with non-biliary acute pancreatitis. All analyses were performed in SPSS 8.0 for Windows.

## **RESULTS**

During the study period 823 cases met our inclusion criteria. After the expert review, 80 eligible cases were excluded as the diagnosis acute pancreatitis could not be substantiated. Furthermore, 19 cases did not have a matched community control and were therefore excluded from the analyses. Among the final 724 cases, 658 (91%) were admitted for a first attack of acute pancreatitis. Three hundred patients had evidence of gallstones and 88 patients had a history of alcohol abuse or used 5 units or more per day. A total of 1791 community controls were matched to the final 724 cases.

A high number of previous hospitalisations, smoking, high intake of alcohol, a his-

**Table 1**  
Patient characteristics

		Cases (n = 724)	Community controls (n = 1791)	OR <sub>unadjusted</sub>
Country	Denmark	69	155	
	Italy	120	151	
	Netherlands	112	112	
	Sweden	423	1373	
Male		422	930	
Age (years)		62.7 (SD 11.7)	60.6 (SD 11.9)	
BMI		25.7 (SD 4.1)	25.2 (SD 3.7)	
	< 18.5	10	25	1.2 (0.6-2.7)
	≥ 18.5 - < 25	328	895	ref.
	≥ 25 - < 30	288	663	1.1 (0.9-1.4)
	≥ 30	90	185	1.3 (0.9-1.7)
	Unknown	8	23	
No. Hosp. *	0	78	250	ref.
	1	148	387	1.3 (0.9-1.8)
	2	139	337	1.3 (0.9-1.8)
	3	97	270	1.2 (0.8-1.7)
	4	80	195	1.4 (0.9-2.0)
	≥ 5	181	349	1.7 (1.3-2.4)
	Unknown	1	3	
Smoking †	0	509	1343	ref.
	1-10	67	197	0.9 (0.7-1.3)
	11-20	116	196	1.7 (1.3-2.2)
	≥ 21	29	37	2.0 (1.1-3.4)
	Unknown	3	18	
Alcohol use ‡	0	152	276	1.3 (0.97-1.6)
	1-7	321	927	ref.
	8-28	181	526	0.8 (0.7-1.1)
	29-49	24	43	1.2 (0.7-2.1)
	≥ 50	40	6	15.3 (5.9-39.9)
	Unknown	6	13	
ADR §		199	539	1.1 (0.9-1.3)
Knowledge on ADR ¶		33	196	0.4 (0.3-0.6)
Gall tract diseases	≤ 1 yr.	34	8	11.7 (5.3-25.8)
	2-5 yr.	18	12	3.5 (1.6-7.8)
	> 5 yr.	75	179	1.2 (0.9-1.6)
Hyperlipidemia §		49	70	1.7 (1.2-2.5)
Ulcer pepticum §		92	114	2.0 (1.5-2.8)
Renal failure §		8	9	1.9 (0.7-5.2)
Inflammatory bowel disease §		9	14	2.2 (0.9-5.1)
Pancreas diseases §		52	9	13.8 (6.4-29.2)
Diabetes mellitus §		70	77	2.1 (1.5-3.0)
Psychosis §		2	5	1.1 (0.2-5.7)
Depression §		74	152	1.3 (0.98-1.8)
Vitamin C **		44	130	0.9 (0.6-1.3)

OR=odds ratio, SD=standard deviation, BMI=body mass index, ADR=adverse drug reaction, \* Number of hospitalisations in entire life, † number of cigarettes smoker per day, ‡ Units of alcohol per week, § Ever history of, ¶ Knowledge that drugs may cause acute pancreatitis, \*\* use in the week before the index date.

**Table 2**

Association between use of TCAs, SSRIs, benzodiazepines, antipsychotics and acute pancreatitis.

Drug*	Cases (n = 724)	Community controls (n = 1791)	OR <sub>adjusted</sub> <sup>†</sup>
TCA	12	18	1.7 (0.8-4.0)
SSRI	19	28	1.7 (0.9-3.3)
Benzodiazepines	68	104	1.3 (0.9-1.9)
Antipsychotics	20	20	3.0 (1.5-6.0)
Age 40-59 years	6	10	1.3 (0.4-4.6)
60-85 years	14	10	4.1 (1.7-9.9)

TCA = tricyclic antidepressant, SSRI = selective serotonin reuptake inhibitor, \*use in the week before the index date, † adjusted for alcohol use, smoking, history of pancreatic, history of biliary disease, history of diabetes mellitus

tory of biliary disease, hyperlipidemia, peptic ulcer disease, diabetes mellitus, and pancreatic disease were all positively associated with development of acute pancreatitis (table 1).

Use of TCAs, SSRIs, and benzodiazepines all showed a modest, non-significantly increased risk of acute pancreatitis (table 2). Short- and long acting benzodiazepines had similar risk estimates for acute pancreatitis. Use of antipsychotic drugs in the week prior to the index date showed an increased relative risk of 3.0 (95% CI: 1.5-6.0). The risk of acute pancreatitis associated with antipsychotics was largely confined to elderly patients (table 2). It was not possible to assess the risk of atypical antipsychotics separately as only three cases and no controls used an atypical antipsychotic. Data on dispensed prescriptions of antipsychotics showed that reported data on antipsychotics was complete in the Netherlands for both cases and controls. The numbers were too low to assess dose- and duration responses. Restriction of the analysis to patients with a first attack of acute pancreatitis did not change the results.

## DISCUSSION

In this multinational study on drug-induced acute pancreatitis, we demonstrated that use of antipsychotics was associated with an increased risk of acute pancreatitis and that this risk was largely confined to elderly patients.

Several case-reports have suggested a causal relationship between use of the antidepressants and acute pancreatitis. Both TCAs(6-10) and SSRIs(11) have been incriminated. Clomipramine-, imipramine-, amoxapine-, and maprotiline-induced acute pancreatitis is briefly mentioned in two surveys from spontaneous reporting centres.(9,10) Two reports mention acute pancreatitis after deliberate overdoses of amoxapine and clomipramine.(7,8) However, both patients used other drugs con-

comitantly and both had other conditions that might explain elevated enzyme levels. None of the patients were rechallenged with the suspected antidepressant. Reports on antipsychotic-associated acute pancreatitis concerned the atypical agents clozapine, olanzapine, and risperidone.(12-21). Two patients had a return of abdominal pain on restarting clozapine, but serum amylase was not measured in one patient and the other had concomitant cholelithiasis.(15,23) As our study ended in 1998, only three cases and none of the controls used an atypical antipsychotic, hence it was not possible to estimate risks for typical and atypical antipsychotics separately.

The mechanism by which antipsychotic drugs may cause acute pancreatitis is unknown. Drugs may cause acute pancreatitis by an allergic reaction. However, rash was not reported in any of the patients and hypereosinophilia was only reported in 2 patients.(15,23) Alternatively, drugs may induce other risk factors for acute pancreatitis. For instance, vitamin D intoxication predisposes to hypercalcemia,(24) fibrates may induce cholelithiasis,(25) and estrogens may lead to hypertriglyceridemia.(26) Hypercalcemia, cholelithiasis, and hypertriglyceridemia are known causes of acute pancreatitis. Increased triglyceride levels are associated with use of antipsychotics.(27) Dopamine had an anti-inflammatory effect in an animal model of acute pancreatitis. This anti-inflammatory effect was antagonised by simultaneous haloperidol administration.(28) This may provide a rationale for the increased risk of pancreatitis associated with use of antipsychotics.

Most information on drug-associated acute pancreatitis is derived from anecdotal reports. Our study is unique in its size and its aim to quantify the risk of acute pancreatitis. However, one must consider the results of our study in light of its potential limitations. We limited underascertainment of potential cases by using standardised and objective screening criteria. Although mild cases may have been missed, symptomatic cases of acute pancreatitis are mostly recognised and admitted irrespective of the suspected aetiology, hence selection bias is unlikely. Diagnostic bias due to diagnosing acute pancreatitis more easily in patients who use psychotropic drugs is not likely due to the acute nature of the disease, the screening procedures that we used, and due to the widespread belief that drugs have a low attributable risk for acute pancreatitis. In addition, all cases were validated by experts who were blinded to exposure.

Information bias regarding exposure is a particular problem in case-control studies as cases might recall drug use more accurately than controls due to their recent illness. However, verification at community pharmacies in the Netherland showed that data on use of antipsychotic drugs was complete for both cases and controls. We studied the influence of recall bias by including a question on use of vitamin C (not known to be associated with acute pancreatitis) and by asking whether participants knew that drugs may cause acute pancreatitis. Vitamin C was not associated with development of acute pancreatitis and slightly more controls than cases knew that drugs may be a possible cause of acute pancreatitis. These findings suggest that recall bias did not a

play a major role in our study.

In our analyses we adjusted for smoking, alcohol abuse, a history of biliary diseases, a history of diabetes, and a history of pancreatic diseases. We had no information on the presence of gallstones in controls at the time of interview. Therefore we adjusted for a history of biliary diseases which was strongly associated with an increased risk of acute pancreatitis. Alcohol use may be an important confounder in the relationship between psychotropic drugs and acute pancreatitis. We adjusted for alcohol use in our analysis, but residual confounding due to underascertainment of alcohol exposure can not be excluded with certainty. However, misclassification of alcohol exposure is only of importance in distinguishing alcohol abuse from modest alcohol consumption as our analyses showed an increased risk for high alcohol consumption only.

In conclusion, antipsychotic drugs were associated with an increased risk of acute pancreatitis and should be considered as a potential cause in patients with acute pancreatitis.

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The risk of acute pancreatitis  
associated with the use of fibrates

4.4

**Acute pancreatitis associated with the use of fibrates:  
The European case-control study on drug-induced acute pancreatitis (EDIP)**

*Introduction:* Fibrates and hydroxymethylglutaryl-co-enzym-A (HMG-Co-A) reductase inhibitors have both been associated with acute pancreatitis. We quantified the risk of acute pancreatitis associated with use of lipid lowering drugs in the European study on drug-induced acute pancreatitis (EDIP).

*Methods:* The EDIP study is a multi-centre population-based European case-control study on the association between drug use and acute pancreatitis. Patients between 40 and 85 years of age with acute pancreatitis were included between October 1st 1994 and December 31st 1998. Age- and gender-matched community controls were recruited for each case. Detailed information on drug use and potential confounders (e.g. co-morbidity, alcohol use) was obtained through a structured interview.

*Results:* During the study period, we identified and interviewed 724 patients with acute pancreatitis and 1791 community controls. A high number of previous hospitalisations, smoking, high intake of alcohol, a history of biliary disease, hyperlipidemia, peptic ulcer disease, and pancreatic disease were positively associated with development of acute pancreatitis. Use of fibrates in the week before the index date was associated with a 3.5 fold increase in the risk of acute pancreatitis (95% CI: 1.4-9.2). Use of HMG-CoA-reductase inhibitors was not associated with an increased risk of acute pancreatitis.

*Conclusion:* Use of fibrates is associated with an increased risk of acute pancreatitis.

## INTRODUCTION

Acute pancreatitis is an inflammatory disease of the pancreas which may lead to considerable morbidity and mortality. The incidence of acute pancreatitis shows an increasing trend in European countries.(1,2) The most important risk factors for acute pancreatitis are gallstones and alcohol abuse. Other risk factors include hyperlipidemia, hypercalcemia, and endoscopic retrograde cholangiopancreatography (ERCP). The etiology remains unknown in 10 to 25% of patients with acute pancreatitis.(3)

Drugs have since long been implicated as a potential cause of acute pancreatitis.(4) However, most information on drug-induced acute pancreatitis is derived from anecdotal case-reports and little is known about the incidence and mechanisms of drug-induced acute pancreatitis.(5)

Acute pancreatitis has been associated with fibrates,(6-10) hydroxymethylglutarylco-enzym-A (HMG-Co-A) reductase inhibitors, (11-18) and combined use of these two drug classes.(11,19) In addition cholestyramine-associated acute pancreatitis has been described.(12,20)

We assessed the risk of acute pancreatitis associated with use of lipid lowering drugs in the European study on drug-induced acute pancreatitis (EDIP).

## METHODS

### Setting

This study is part of the European case-control study on drug-induced acute pancreatitis (EDIP), which was initiated by the European Pharmacovigilance Research Group. Participating countries include Denmark, Italy, the Netherlands, Portugal, Sweden, and the United Kingdom. The source population comprised all persons between 40 to 85 years of age in the county of Funen in Denmark, the Rijnmond area in the Netherlands, the Coimbra area in Portugal, the cities Malmö, Stockholm, Uppsala, and Umeå in Sweden, the cities Bologna, Bolzano, Milano, and Verona in Italy, and Birmingham city in the United Kingdom. For the present study only data from Denmark, the Netherlands, Italy, and Sweden was used because of absence of data on community controls in the other countries. The study period ran from October 1st 1994 to December 31st 1998, but differed in the participating countries. Local medical ethical committees approved the study, and written informed consent was obtained from all participants.

## Case identification and validation

In the Netherlands, Sweden, and Denmark potential cases were identified by regular screening of serum amylase and lipase values of admitted patients in the participating hospitals. In Italy, the departments of internal medicine, gastroenterology, and surgery were regularly screened for patients admitted with acute abdominal pain. Patients were considered potential cases of acute pancreatitis if they had acute abdominal pain combined with elevated serum amylase and lipase values of more than 2 times the upper limit of normal within the first week of admission, or if they had acute abdominal pain with confirmatory evidence of acute pancreatitis on ultrasonography, computerized tomography, laparotomy, or autopsy. Patients with post-ERCP pancreatitis, abdominal trauma, a perforated gastrointestinal ulcer, malignancy of the gastrointestinal tract, a positive HIV test, or chronic pancreatitis were excluded. Additionally, patients were excluded if they were resident in a nursing home, did not speak the native language, died before study assessments were completed, or if no reliable interview data could be obtained (e.g. due to dementia). Since Sweden combined the EDIP study with a national study, their exclusion criteria were slightly different in the cities Stockholm and Umeå. In these cities, patients with a history of biliary diseases and patients with a relapse of acute pancreatitis were also excluded. Acute pancreatitis was considered of biliary origin if gallstones were present at imaging procedures or at laparotomy.

The clinical notes of all eligible cases were reviewed by consultant gastroenterologists who were blinded to drug exposure. The index date for the cases was defined as the date of first recorded symptoms.

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In Sweden, Denmark, and Italy community controls were randomly selected from population registries. Community controls were randomly selected from the general practitioner's practice of the case in the Netherlands. Controls were matched to cases on gender and age ( $\pm 5$  years). The index date of the controls was defined as the date of interview. Exclusion criteria for controls were equal to exclusion criteria for cases.

## Data collection

Each country used similar structured questionnaires and coding manuals (International Classification of Diseases, 9th edition and the Drug Dictionary of the World Health Organization). Interviewers were centrally trained and supervised. The questionnaire included questions on demographics, life-long medical history, smoking and drinking habits, plus drug intake in the preceding six months. In order to reduce

recall bias, participants were asked to retrieve all packages of drugs that they had used before start of the interview. For each drug, the indication, strength, formulation, dosing regimen, start and stop dates were recorded.

## **Exposure**

Use of fibrates was defined as use of fenofibrate, bezafibrate, ciprofibrate, and gemfibrozil in the week before the index date. Use of HMG-CoA-reductase inhibitors was defined similarly as use of simvastatin, lovastatin, fluvastatin, pravastatin, and atorvastatin. To study potential recall bias, we verified use of lipid lowering drugs at the community pharmacy of the study participants in the Netherlands.

## **Covariates**

As potential confounders we considered smoking, alcohol use, and co-morbidity. Smoking was expressed as the number of cigarettes smoked per day: 0, 1-10, 11-20, and more than 21. Alcohol use was expressed as the average intake of units of alcohol per day: 1 unit, 2-4 units, 5-7 units, and 8 or more units. Weight categories were created on the basis of body mass index (BMI): underweight (<18.5), normal ( $\geq 18.5 - < 25$ ), overweight ( $\geq 25 - < 30$ ), and obese ( $\geq 30$ ).<sup>(21)</sup> Working status was divided into employed, ill, unemployed, student or military service, and other.

## **Analyses**

Maximum likelihood estimates of odds ratios (ORs) and their 95% confidence intervals (CIs) were computed using a conditional logistic regression model. In the multivariate analyses risk estimates for use of fibrates and HMG-CoA-reductase inhibitors were adjusted for alcohol use, smoking, BMI, index year (1994-1996 and 1997-1998), history of pancreatic disease, history of biliary disease, and history of diabetes mellitus. We performed additional analyses restricted to patients with a first attack of acute pancreatitis and patients with non-biliary acute pancreatitis. All analyses were performed in SPSS 8.0 for Windows.

## **RESULTS**

During the study period 823 cases met our inclusion criteria. Eighty cases were excluded after expert review, as the diagnosis acute pancreatitis could not be substantiated. Furthermore, 19 cases did not have a matched community control and were therefore excluded from the analyses. Among the final 724 cases, 658 (91%) were

**Table 1**  
Patient characteristics

		Cases (n = 724)	Community controls (n = 1791)	OR <sub>unadjusted</sub>
Country	Denmark	69	155	
	Italy	120	151	
	Netherlands	112	112	
	Sweden	423	1373	
Male		422	930	
Age (years)		62.7 (SD 11.7)	60.6 (SD 11.9)	
BMI		25.7 (SD 4.1)	25.2 (SD 3.7)	
	< 18.5	10	25	1.2 (0.6-2.7)
	≥ 18.5 - < 25	328	895	ref.
	≥ 25 - < 30	288	663	1.1 (0.9-1.4)
	≥ 30	90	185	1.3 (0.9-1.7)
	Unknown	8	23	
No. Hosp. *	0	78	250	ref.
	1	148	387	1.3 (0.9-1.8)
	2	139	337	1.3 (0.9-1.8)
	3	97	270	1.2 (0.8-1.7)
	4	80	195	1.4 (0.9-2.0)
	≥ 5	181	349	1.7 (1.3-2.4)
	Unknown	1	3	
Smoking †	0	509	1343	ref.
	1-10	67	197	0.9 (0.7-1.3)
	11-20	116	196	1.7 (1.3-2.2)
	≥ 21	29	37	2.0 (1.1-3.4)
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Alcohol use ‡	0	152	276	1.3 (0.97-1.6)
	1-7	321	927	ref.
	8-28	181	526	0.8 (0.7-1.1)
	29-49	24	43	1.2 (0.7-2.1)
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ADR §		199	539	1.1 (0.9-1.3)
Knowledge on ADR ¶		33	196	0.4 (0.3-0.6)
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	2-5 yr.	18	12	3.5 (1.6-7.8)
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Hyperlipidemia §		49	70	1.7 (1.2-2.5)
Ulcer pepticum §		92	114	2.0 (1.5-2.8)
Renal failure §		8	9	1.9 (0.7-5.2)
Inflammatory bowel disease §		9	14	2.2 (0.9-5.1)
Pancreas diseases §		52	9	13.8 (6.4-29.2)
Diabetes mellitus §		70	77	2.1 (1.5-3.0)
Vitamin C **		44	130	0.9 (0.6-1.3)

OR = odds ratio, SD = standard deviation, BMI = body mass index, ADR = adverse drug reaction, \* Number of hospitalisations in entire life, † number of cigarettes smoker per day, ‡ Units of alcohol per week, § Ever history of, ¶ Knowledge that drugs may cause acute pancreatitis, \*\* use in the week before the index date.

**Table 2**

Association between use of fibrates and acute pancreatitis.

	Cases (n = 724)	Community controls (n = 1791)	OR <sub>adjusted</sub> †
Fibrates*	14	10	3.5 (1.4-9.2)
Bezafibrate	5	1	15.2 (1.4-159.7)
Gemfibrozil	8	9	1.9 (0.6-5.8)
HMG CoA red.	27	48	1.1 (0.7-2.0)
Inhibitors*			
Simvastatin	21	35	1.1 (0.6-2.1)
Pravastatin	4	3	3.7 (0.4-32.7)
Fluvastatin	2	6	1.5 (0.3-8.2)

OR=odds ratio, HMG CoA red = hydroxymethylglutaryl-co-enzym-A reductase, \*use in the week before the index date, † adjusted for alcohol use, smoking, bmi, index year, history of pancreatic disease, history of biliary disease, history of diabetes mellitus.

admitted for a first attack of acute pancreatitis. Three hundred (41%) patients had evidence of gallstones and 88 (12%) patients had a history of alcohol abuse or used 5 units or more per day. A total of 1791 community controls were matched to the final 724 cases.

A high number of previous hospitalisations, smoking, high intake of alcohol, and a history of biliary disease, hyperlipidemia, peptic ulcer disease, diabetes mellitus and pancreatic disease were all positively associated with development of acute pancreatitis (table 1).

Use of fibrates in the week prior to the index date was associated with an increased risk of acute pancreatitis with an adjusted OR of 3.5 (95% CI: 1.4-9.2). Restriction to patients with a first attack of acute pancreatitis did not change the results. The risk of acute pancreatitis during use of fibrates seemed higher in patients aged 60 years and over with an OR of 5.4 (95% CI: 1.4-20.1), in patients without biliary disease with an OR of 19.7 (2.0-192.9), and in users of bezafibrate with OR of 15.2 (95% CI: 1.4-159.7), but numbers were low. Use of HMG-CoA-reductase inhibitors did not increase the risk of acute pancreatitis and did not modify the risk of fibrates since only 4 patients used fibrates and HMG-CoA-reductase inhibitors together. Since most of the fibrates were prescribed for a similar dose and all patient currently using fibrates used fibrates for a longer period of time we could not assess dose and duration response relationships. The risk of acute pancreatitis associated with bile acid binders and nicotinic acid derivatives could not be estimated due to low exposure prevalence. Data on dispensed prescriptions of fibrate at community pharmacies in the Netherlands showed that reported data on fibrate use was complete for controls. One case had filled a prescription for fibrate, while fibrate use was not reported in the interview.

## DISCUSSION

In this multinational study we found an increased risk of acute pancreatitis in users of fibrates. The risk of acute pancreatitis associated with fibrate seemed higher in elderly patients. Use of HMG-CoA-reductase inhibitors was not associated with an elevated risk of acute pancreatitis.

Acute pancreatitis has been attributed to fibrates in the literature, but to our knowledge epidemiological studies on this subject have not been performed.(6-10) Prompt recurrence of pancreatitis occurred twice after restart of bezafibrate in one reported patient, suggesting a potential allergic reaction.(9) Secondary biliary pancreatitis may be an alternative mechanism for fibrate-associated acute pancreatitis, as fibrates are capable of inducing cholelithiasis.(22) However, our study does not confirm this mechanism as the risk was higher after exclusion of patients with biliary pancreatitis.

Acute pancreatitis has been attributed to HMG-CoA-reductase inhibitors, but detailed rechallenge studies have not been described. (11-13, 15-18) Rhabdomyolysis attributed to HMG-CoA-reductase inhibitors therapy, and in particular to combined use of HMG-CoA-reductase inhibitors and fibrates is well documented (23) and acute pancreatitis secondary to rhabdomyolysis after use of HMG-CoA-reductase inhibitors has been reported.(14,19)

The results of our study should be interpreted in light of potential limitations which can be classified as selection, information and confounding bias. Selection bias is limited since both diagnostic bias and underascertainment bias are low. We limited underascertainment of potential cases by using standardised and objective screening criteria. Although mild cases may have been missed, symptomatic cases of acute pancreatitis are mostly recognised and admitted irrespective of the suspected aetiology. Diagnostic bias due to diagnosing acute pancreatitis more easily in patients who use fibrates is not likely due to the acute nature of the disease, the screening procedures that we used, and due to the widespread belief that drugs have a low attributable risk for acute pancreatitis. In addition, all cases were validated by experts who were blinded to exposure.

Information bias regarding exposure is a particular problem in case-control studies as cases might recall drug use more accurately than controls due to their recent illness. However, data on dispensed prescriptions of fibrates at community pharmacies in the Netherlands showed that data on fibrate use was complete for controls. In addition, we studied the influence of recall bias by including a question on use of vitamin C (not known to be associated with acute pancreatitis) and by asking whether participants knew that drugs may cause acute pancreatitis. Vitamin C was not associated with development of acute pancreatitis and slightly more controls than cases knew that drugs may be a possible cause of acute pancreatitis. These findings suggest that

recall bias did not play a major role in our study.

Confounding by indication is a particular problem when assessing the relation between fibrates and acute pancreatitis. Hyperlipidemia may induce acute pancreatitis, but only at grossly elevated levels.(24) In our study confounding by indication cannot be excluded as a possible explanation for the observed relationship.

In our analyses we adjusted for smoking, alcohol abuse, a history of biliary diseases, a history of diabetes, and a history of pancreatic diseases. We had no information on the presence of gallstones in controls at the time of interview. Therefore we adjusted for a history of biliary diseases which was strongly associated with an increased risk of acute pancreatitis. Alcohol use may induce hyperlipidemia with subsequent prescription of lipid lowering drugs. We adjusted for alcohol use in our analysis, but residual confounding due to underascertainment of alcohol exposure can not be excluded. However, misclassification of alcohol exposure is only of importance in distinguishing alcohol abuse from modest alcohol consumption as our analyses showed an increased risk for high alcohol consumption only.

In conclusion, fibrates were associated with an increased risk of acute pancreatitis and should be considered as a potential cause in patients with acute pancreatitis.

## **ACKNOWLEDGEMENTS**

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Monitor: T. Murphy

\* European Pharmacovigilance Research Group coordinator: Professor Sir M.D. Rawlins.

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The risk of acute pancreatitis  
associated with the use of vitamin D

4.5

**Acute pancreatitis associated with the use of vitamin D:  
The European case-control study on drug-induced acute pancreatitis (EDIP)**

*Introduction:* Use of vitamin D may induce hypercalcemia, which is a risk factor for acute pancreatitis. We investigated the association between vitamin D use and acute pancreatitis in the European study on drug-induced acute pancreatitis (EDIP)

*Methods:* The EDIP study is a multi-centre population-based European case-control study on the association between drug use and acute pancreatitis. Patients between 40 and 85 years of age with acute pancreatitis were included between October 1st 1994 and December 31st 1998. Age- and gender-matched community controls were recruited for each case. Detailed information on drug use and potential confounders (e.g. co-morbidity, alcohol use) was obtained through a structured interview.

*Results:* During the study period, we identified and interviewed 724 patients with acute pancreatitis and 1791 community controls. A high number of previous hospitalisations, smoking, high intake of alcohol, a history of biliary disease, hyperlipidemia, peptic ulcer disease, and pancreatic disease were positively associated with development of acute pancreatitis. Use of vitamin D in the week before the index date was associated with a 3.5 fold increase in the risk of acute pancreatitis (95% CI: 1.01-12.2).

*Conclusion:* Vitamin D use is associated with an increased risk of acute pancreatitis, possibly might be explained by vitamin D induced hypercalcemia.

## INTRODUCTION

Acute pancreatitis is an inflammatory disease of the pancreas which may lead to considerable morbidity and mortality. The incidence of acute pancreatitis shows an increasing trend in European countries.(1,2) The most important risk factors for acute pancreatitis are gallstones and alcohol abuse. Hypercalcemia is another risk factor for acute pancreatitis.(3) Acute pancreatitis due to hypercalcemia has been described in patients with hyperparathyroidism, sarcoidosis, malignancy, myeloma, and in a patient with vitamin D intoxication.(4-8) We assessed the risk of acute pancreatitis associated with use of vitamin D in the European study on drug-induced acute pancreatitis (EDIP).

## METHODS

### Setting

This study is part of the European case-control study on drug-induced acute pancreatitis (EDIP), which was initiated by the European Pharmacovigilance Research Group. Participating countries include Denmark, Italy, the Netherlands, Portugal, Sweden, and the United Kingdom. The source population comprised all persons between 40 to 85 years of age in the county of Funen in Denmark, the Rijnmond area in the Netherlands, the Coimbra area in Portugal, the cities Malmö, Stockholm, Uppsala, and Umeå in Sweden, the cities Bologna, Bolzano, Milano, and Verona in Italy, and Birmingham city in the United Kingdom. For the present study only data from Denmark, the Netherlands, Italy, and Sweden was used because of absence of data on community controls in the other countries. The study period ran from October 1st 1994 to December 31st 1998, but differed in the participating countries. Local medical ethical committees approved the study, and written informed consent was obtained from all participants.

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### **Exposure**

Use of vitamin D analogues was defined as use of these compounds in the week before the index date. Use of multivitamin preparations was not considered in this analysis.

To study potential recall bias, we verified use of vitamin D preparations at the community pharmacy of the participants in the Netherlands.

### **Covariates**

As potential confounders we considered smoking, alcohol use, and co-morbidity. Smoking was expressed as the number of cigarettes smoked per day: 0, 1-10, 11-20, and more than 21. Alcohol use was expressed as the average intake of per day: 1 unit, 2-4 units, 5-7 units, and 8 or more units. Weight categories were created on the basis of body mass index (BMI): underweight (<18.5), normal ( $\geq 18.5 - < 25$ ), overweight ( $\geq 25 - < 30$ ), and obese ( $\geq 30$ ).<sup>(9)</sup> Working status was divided into employed, ill, unemployed, student or military service, and other.

### **Analyses**

Maximum likelihood estimates of odds ratios (ORs) and their 95% confidence intervals (CIs) were computed using a conditional logistic regression model. In the multivariate analysis risk estimates for use of vitamin D preparations were adjusted for alcohol use, smoking, BMI, index year (1994-1996 and 1997-1998), history of pancreatic disease, history of biliary disease, and history of diabetes mellitus. We performed additional analyses restricted to patients with a first attack of acute pancreatitis and patients with non-biliary acute pancreatitis. All analyses were performed in SPSS 8.0 for Windows.

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A high number of previous hospitalisations, smoking, high intake of alcohol, and a history of biliary disease, hyperlipidemia, peptic ulcer disease, diabetes mellitus, and pancreatic disease were all positively associated with development of acute pancreatitis (table 1).

Use of vitamin D in the week prior to the index date was associated with an increased risk of acute pancreatitis: adjusted OR 3.5 (95% CI: 1.01-12.2). The risk of vitamin D associated acute pancreatitis seemed higher in patients without biliary

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Inflammatory bowel disease§		9	14	2.2 (0.9-5.1)
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Vitamin C**		44	130	0.9 (0.6-1.3)

OR = odds ratio, SD = standard deviation, BMI = body mass index, ADR = adverse drug reaction, \* Number of hospitalisations in entire life, † number of cigarettes smoker per day, ‡ Units of alcohol per week, § Ever history of, ¶ Knowledge that drugs may cause acute pancreatitis, \*\* use in the week before the index date.

pancreatitis: OR (24.7 (95% CI: 1.4-424.0), in patients aged 40-60 years: OR 10.3 (95% CI: 1.4-75.1), and in users of hydroxylated vitamin D: OR 13.5 (95% CI: 1.3-143.7), but numbers were low. Adjustment for renal failure did not change the results. None of the users of vitamin D used pancreatic enzymes concomitantly. The exposure prevalence was too low to estimate duration-, and dose response relationships. Data on dispensed prescriptions of vitamin D preparations at community pharmacies in the Netherlands showed that data on vitamin D use was complete.

## DISCUSSION

In this multinational study we found an increased risk of acute pancreatitis in users of vitamin D preparations. The risk of acute pancreatitis associated with vitamin D preparations may be higher in patients using hydroxylated vitamin D.

In the skin, 7-dehydrocholesterol is changed into vitamin D<sub>3</sub> under the influence of sunlight. People with low exposure to sunlight and people with low vitamin D production capacity (blacks, elderly) need dietary vitamin D to maintain adequate vitamin D levels. Vitamin D<sub>3</sub> is hydroxylated to 25-hydroxy-vitamin D<sub>3</sub> in the liver, which is subsequently hydroxylated to 1,25-hydroxy-vitamin D<sub>3</sub> in the kidney. This most active form of vitamin D promotes active absorption of phosphate and calcium in the small intestine. Intoxication with vitamin D leads to hypercalcemia, which is a well-known risk factor for acute pancreatitis. This is especially true for 1-hydroxylated vitamin D<sub>3</sub> since hydroxylation by 1- $\alpha$ -hydroxylase is the rate-limiting step in the production of 1,25-hydroxy-vitamin D<sub>3</sub>.

Acute pancreatitis attributed to vitamin D intoxication has been described in one case-report. This patient had recurrent pancreatitis associated with hypercalcemia, which was precipitated by excessive self-medication with vitamin D preparations. This patient had elevated 25-hydroxy-vitamin D<sub>3</sub> (4.5 x N), reflecting increased body stores of vitamin D. However, he had subnormal levels of 1,25-hydroxy-vitamin D probably due to suppressed 1- $\alpha$ -hydroxylase activity by low PTH levels and high serum phosphate levels.

The results of our study should be interpreted in light of its potential limitations. We limited underascertainment of potential cases by using standardised and objective screening criteria. Although mild cases may have been missed, symptomatic cases of acute pancreatitis are mostly recognised and admitted irrespective of the suspected aetiology. Hence selection bias is unlikely. Diagnostic bias due to diagnosing acute pancreatitis more easily in patients who use vitamin D is not likely due to the acute nature of the disease, the screening procedures that we used, and due to the widespread belief that drugs have a low attributable risk for acute pancreatitis. In addition, all cases were validated by experts who were blinded to exposure.

Information bias regarding exposure is a particular problem in case-control studies as cases might recall drug use more accurately than controls due to their recent illness. However, data on dispensed prescriptions of vitamin D at community pharmacies in the Netherlands showed that data on vitamin D use was complete. In addition, we studied the influence of recall bias by including a question on use of vitamin C (not known to be associated with acute pancreatitis) and by asking whether participants knew that drugs may cause acute pancreatitis. Vitamin C was not associated with development of acute pancreatitis and slightly more controls than cases knew that drugs may be a cause of acute pancreatitis. These findings suggest that recall bias did not play a major role in our study.

Confounding by indication is a particular problem when assessing the relation between vitamin D use and acute pancreatitis. Vitamin D may be prescribed in patients with pancreatic insufficiency due to previous or chronic pancreatitis. In our study, patients with signs of chronic pancreatitis were excluded and we adjusted for history of pancreatitis in our analyses. None of the users of vitamin D used pancreatic enzymes, indicating that none had manifest pancreatic insufficiency. Vitamin D is also prescribed in patients with renal insufficiency to correct secondary hyperparathyroidism. Renal insufficiency has been proposed as a risk factor for acute pancreatitis, but adjusting for renal insufficiency did not change the risk estimates of vitamin D in our analyses.

In conclusion, use of vitamin D was associated with an increased risk of acute pancreatitis and should be considered as a potential cause in patients with acute pancreatitis.

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CHAPTER 5 *five*

*Discussion  
and summary*



Discussion

*5.1*



In this thesis, the objective was to study drugs as a potential cause of acute pancreatitis. Drugs received relatively little attention as a risk factor for acute pancreatitis in the medical literature.(1) In the first part of this thesis, we estimated the incidence and mortality of acute pancreatitis to assess the potential public health impact of our topic. In the second part, we applied several methods and used different sources to study the association between drugs and acute pancreatitis. In the following paragraphs, we will consecutively discuss the incidence and mortality of acute pancreatitis, the different tools for drug safety assessment, and our studies on drug-induced acute pancreatitis.

## **INCIDENCE AND MORTALITY OF ACUTE PANCREATITIS**

The incidence of acute pancreatitis has increased in several developed countries between 1960 and 1985.(2-7) Apart from a real increase in incidence, an alternative explanation for this observation might be the improvement of diagnostic tests for acute pancreatitis. Our nationwide incidence study showed that this increase continued during the period between 1985-1995, despite the unchanged character of diagnostic procedures such as ultrasonography and assessment of serum amylase. Hence, it is likely that the increased incidence of acute pancreatitis is genuine and not explained by better diagnostic procedures. Our study showed that the incidence of acute pancreatitis increased strongly with age, which could not be explained by ageing of the Dutch population since age-standardised incidence rates increased as well. Despite an increasing incidence of acute pancreatitis, overall mortality rates due to acute pancreatitis were stable in the period 1985-1995. The lower case-fatality may be the result of more effective intensive care treatment or to more frequently diagnosing of milder forms of acute pancreatitis (e.g. after ERCP).

Since we intended to study trends over a broad time interval, we used hospital discharge data to study the incidence of acute pancreatitis. Incidence studies based on hospital data, however, may underestimate the true incidence rate if not all patients with acute pancreatitis are referred to hospital. Therefore, we also performed a study on the incidence of acute pancreatitis in a large database with information from general practices. This study showed that 98% of all patients diagnosed with acute pancreatitis by general practitioners were referred to hospital. Consequently, incidence estimates in both studies were of similar magnitude.

The incidence of acute pancreatitis may also be underestimated if autopsy data are ignored.(8, 9) We did not include data from pathology databases in our two incidence studies. However, autopsy data were included indirectly as they are reported to the general practitioner and used for the coding of discharge diagnoses. Hence, it is not likely that we missed more than an incidental case.

In conclusion, the incidence of acute pancreatitis rose in the period 1985-1995. This rise can not be explained by an ageing population, nor by improvement of diagnostic tests. In the study period, the incidence of both biliary diseases and endoscopic procedures increased, both of which may be a potential explanation for the rise in the incidence of acute pancreatitis.

## **TOOLS FOR DRUG SAFETY**

Since pre-marketing studies are primarily designed to investigate efficacy of drugs, they are not able to detect rare adverse events such as acute pancreatitis. Besides the lack of power to detect rare adverse drug reactions, the duration of follow-up is usually too short to detect adverse drug reactions with delayed onset. In addition, most pre-marketing studies are conducted in selected patient groups. Children, elderly, and patients with extensive co-morbidity are usually excluded, whereas these patient groups may have an increased risk of adverse drug reactions.

The limitations of pre-marketing studies emphasize the need for other methods to study adverse drug reactions. Spontaneous reporting of adverse drug reactions to drug monitoring centres has been the mainstay of pharmacovigilance for many years but this system has some limitations. Only a small proportion of adverse drug reactions are notified to monitoring centres, (10) which is true even for severe reactions such as anaphylaxis.(11) Moreover, reports to such centres often lack sufficient data to assess the causal relationship between the suspected drug and the adverse event. Despite these limitations, the important advantage of these systems is their potential to generate signals of new and severe adverse drug reactions.

Often, observed adverse reactions are not reported to monitoring centres but published in the medical literature. Such case-reports may provide even more important signals on adverse drug reactions thanks to their detailed descriptions of individual case histories. However, in the absence of rechallenge it may be difficult to draw conclusions on the causal relationship.

The signals provided by spontaneous reporting systems and by reports in the literature may be the start of subsequent analytical pharmacoepidemiological studies. On first thought, a post-marketing clinical trial may seem the ideal method for quantification of a potential adverse drug reaction. However, if one requires 90% power ( $\alpha < 0.05$ ;  $\beta = 0.1$ ) to detect a relative risk as high as 3.0 for the association between a certain drug and acute pancreatitis (assuming a background incidence of 0.015%), one would need to randomise over 100,000 patients. A post-marketing trial of that size is clearly too expensive to perform. Observational (= non-experimental) pharmacoepidemiological studies are, therefore, essential in assessing the risks of rare adverse reactions such as acute pancreatitis. The validity of observational studies is frequently

questioned because of potential bias and confounding but a careful design may deal with most of these problems. The two main observational approaches in pharmacoepidemiology follow cohort and case-control designs. In the cohort design, the frequency of the adverse reaction is compared between patients with and without the exposure of interest. The advantages of this study design are the direct measurement of the incidence of the adverse event, prospective assessment of exposure, which avoids recall bias, and its suitability to study adverse reactions to infrequently used drugs. However, the studied adverse event needs to be rather frequent. Since acute pancreatitis is a rare event, cohort studies are usually not an efficient approach to study associations between drugs and acute pancreatitis.

In pharmaco-epidemiological case-control studies, drug exposure is compared between patients with and without the adverse event. The case-control design is an efficient design to study rare adverse reactions, as drug exposure is only measured in patients with the adverse event and in a sample of the source population. Another advantage of the case-control design in studying drug-associated acute pancreatitis is its suitability to study multiple drug exposures. However, case-control studies are less suitable to study rare drug exposures, as drug exposure in controls may be too low to validly estimate risks. An important limitation of case-control studies is their vulnerability to bias. Inclusion of cases and controls may depend on exposure status (selection bias) and patients with the disease may recollect former drug exposure more accurately than controls due to their recent disease (recall bias). This form of information bias is absent if prospectively recorded data on exposure are used.

Many of the advantages and disadvantages of the different study designs depend on the system of data collection. In pharmaco-epidemiological research, two types of data sources can be distinguished. One source concerns the use of computerised databases which consist of billing data or electronic patient records. An example of the latter is the General Practice Research Database (GPRD) which contains medical data on more than four million residents in the United Kingdom. The GPRD has proven to be useful for pharmaco-epidemiological research since it allows for the study of rare adverse drug reactions. Since the data are collected prospectively during general practitioner visits and recorded in a database, studies can be performed in a relatively short time. This is of special value in pharmaco-epidemiology, as drug safety questions often need quick answers. Second, data on drug use is prospectively collected, irrespective of and before the adverse event occurred and therefore selection bias and information bias are limited.

A potential problem with database studies concerns adjustment for other risk factors. Automated databases usually have no information on alcohol use and smoking and these factors may be important confounders in the association between drugs and acute pancreatitis. De novo data collection in an epidemiological field study may overcome this lack of information on important risk factors. A field study has the

advantage that one can assess potential confounders, but has the disadvantage that it is timely and costly. Since adverse drug reactions usually have a low frequency, the case-control design is mostly followed. Another advantage of the case-control design in pharmaco-epidemiological field studies is that ad hoc case-control studies take less time to perform than ad hoc cohort studies.

## **DRUG-INDUCED ACUTE PANCREATITIS**

Drugs as a potential risk factor for acute pancreatitis have received relatively few attention, and little is known about which drugs are associated with acute pancreatitis. We started our exploration of drug-induced acute pancreatitis with the evaluation of spontaneous reports of drug-induced acute pancreatitis and a review of the literature. On the basis of these studies, we quantified the association between five different drug classes and acute pancreatitis.

### **Descriptive studies**

Over 7000 reports of drug-associated acute pancreatitis have been sent to the World Health Organisation. To assess the usefulness of spontaneous reports on drug-induced acute pancreatitis we obtained additional clinical information on all reports notified to the Netherlands Center for Monitoring of Adverse Reactions to Drugs of the Inspectorate for Health Care and to the Netherlands Pharmacovigilance Foundation LAREB. In 11 of the 55 reports, there was insufficient evidence for the diagnosis acute pancreatitis and in another 10 the causal relationship between the suspected drug and acute pancreatitis was unlikely. This shows that thorough evaluation of spontaneous reports and evaluation of additional clinical information is essential before inferences on any kind of frequency or association can be made. One of the evaluated reports concerned acute pancreatitis attributed to interferon- $\alpha$ . This patient and another patient both experienced a relapse of acute pancreatitis after rechallenge. The case-histories of these two patients were prescribed in more detail in a gastroenterological journal to alert medical doctors to interferon- $\alpha$  as a potential cause of acute pancreatitis.

Many reports in the medical literature have suggested an association between individual drugs and acute pancreatitis.<sup>(12)</sup> We performed an extensive literature search to summarise the current knowledge on drug-induced acute pancreatitis. Over 150 individual drugs and drug classes have been suggested as a potential cause of acute pancreatitis. For several reasons, assessment of the causal relationship between suspected drugs and acute pancreatitis in these reports is complicated. Many reports have insufficient data and in reports with complete information a 'chance' association is difficult to exclude if rechallenge was not performed. Information on rechallenge is

sparse since it is only ethical when it concerns a drug which is essential for the treatment of the patient. In some conditions, drug effects may be difficult to separate from the underlying condition for which they were prescribed (confounding by indication). For instance, mesalazine and azathioprine are used in the treatment of inflammatory bowel disease, a disease which increases the risk of acute pancreatitis itself. Prescription of drugs for unrecognised prodromal signs of acute pancreatitis (protopathic bias) may further complicate assessment of the causal relationship between drugs and acute pancreatitis. This bias may, for instance, explain the suggested association between H<sub>2</sub>-blocker and acute pancreatitis. Despite these problems, some reports strongly suggest a causal relationship for a number of drugs. Didanosine-induced acute pancreatitis, for instance, was reported as soon as the first dose escalating studies were performed and it has consistently been reported since then. For some drugs, a causal relationship with acute pancreatitis is certain despite a low incidence. The causal relationship between ACE-inhibitors, azathioprine, and metronidazole has been confirmed by several well-documented rechallenges. However, as mentioned above case-reports do not permit quantification of the risk of acute pancreatitis.

### **Analytical studies**

Based on the descriptive studies, we quantified the association between five different drug classes and acute pancreatitis. Our first study, which was conducted in the GPRD, concerned anti-ulcer drugs as a potential cause of acute pancreatitis. In assessing the association between anti-ulcer drugs and acute pancreatitis, some methodological issues require special attention. Indications (e.g. ulcers) for which anti-ulcer drugs are prescribed may be associated with an increased risk of acute pancreatitis. We limited confounding by indication by selecting a cohort of patients who ever used an anti-ulcer drug and thus ever had an indication for use of these drugs. Anti-ulcer drugs can also be prescribed for unrecognised prodromal signs of acute pancreatitis, which could explain an association between these drugs and acute pancreatitis. We tried to reduce this form of bias by taking the day of onset of symptoms as index date for patients with acute pancreatitis. This is, however, difficult in the GPRD, as prodromal symptoms may not always have been registered in the database. To limit confounding, we restricted our study to people without major risk factors for acute pancreatitis. We should, however, acknowledge that the success of this approach depends on the completeness of pre-recorded information on these confounders. Recording of biliary diseases may be near complete, but alcohol abuse may be recorded less accurately.

To avoid the problems related to control of confounding in database studies, a multinational case-control field study on drug-induced acute pancreatitis was initiated in 1996. This European case-control study on drug-induced acute pancreatitis was performed simultaneously in Denmark, Italy, the Netherlands, Portugal, Sweden,

and the United Kingdom. In the studies prescribed in this thesis, drug use in patients with acute pancreatitis was compared to controls who were randomly selected from the community. In these studies, data from Portugal and the United Kingdom was not used since they ascertained hospital controls.

Adverse reactions may be more easily diagnosed if patients use drugs that are widely known as a potential cause (diagnostic bias). This type of bias is, however, unlikely for acute pancreatitis since the symptoms merit prompt medical care independent of aetiology. In addition, drugs are generally believed to have a low attributable risk for acute pancreatitis and are thus not among the first etiological factors sought. Recall bias is the most important form of information bias in case-control studies that rely on interview as source of information. Compared to community controls, patients with acute pancreatitis may remember former drug use more accurately due to their recent illness. Use of pharmacy dispensing data or GP prescription data prevents recall bias, but has the disadvantage that 'over the counter' drugs are missed and that non-compliance is not taken into account. Since pharmacy dispensing data were not available in all participating countries, we relied on interview to assess drug exposure. We studied the influence of recall bias by including a question on use of vitamin C (not known to be associated with acute pancreatitis) and by asking whether participants knew that drugs may cause acute pancreatitis. Vitamin C was not associated with development of acute pancreatitis and slightly more controls than cases knew that drugs may be a potential cause of acute pancreatitis. In the field study data from the Netherlands, pharmacy dispensing data were compared to drug exposure data derived from interview. Interview data were virtually complete for the drugs we studied: ACE-inhibitors, psychotropic drugs, lipid lowering drugs, and vitamin D. These findings suggest that recall bias did not play a major role in our studies. Confounding is the third aspect that deserves attention in pharmacoepidemiological studies. Alcohol abuse is an important risk factor for acute pancreatitis and may be associated with use of certain drug classes. One of the main advantages of the EDIP field study above the GPRD study is the availability of more accurate data on alcohol use. Apart from the fact that this allows for the study of a dose-relationship between alcohol use and acute pancreatitis, we were able to control for the potentially confounding effect of alcohol. However, one has to bear in mind that residual confounding due to misclassification of alcohol use can never be excluded. Gallstones are an important risk factor for acute pancreatitis as well and may be a confounder if associated with drug use. Since we used community controls to provide us information about the exposure prevalence in the source population, we had no imaging information on the presence of gallstones in controls at the time of interview. Therefore, we were only able to adjust for a history of biliary diseases.

Confounding by indication is a particular problem in pharmacoepidemiological studies. The indication for which a drug is prescribed may be an independent risk factor for acute pancreatitis, thereby explaining an association between the prescribed

drug and development of acute pancreatitis. Confounding by indication probably did not play a major role in our studies on ACE-inhibitor-associated pancreatitis and anti-psychotic drug-associated pancreatitis since hypertension, congestive heart failure, and psychotic disorders are not established risk factors for acute pancreatitis. Hyperlipidemia is a risk factor for acute pancreatitis and confounding by indication could therefore play a role in our study on fibrate-associated acute pancreatitis. Among other indications, vitamin D is prescribed to patients with pancreatic insufficiency and to patients with renal failure. Pancreatic insufficiency may be due to previous pancreatitis, which could predispose to subsequent relapses. However, none of the patients using vitamin D preparations used pancreatic enzymes concomitantly, indicating that none of them had overt pancreatic insufficiency. Moreover, we adjusted for a history of pancreatic diseases in the analyses. Renal failure has been suggested as a potential cause of acute pancreatitis, but adjustment for history of renal failure had no effect on the risk estimate and is therefore unlikely to explain the association between vitamin D and acute pancreatitis.

The lack of quantitative studies on drug-associated acute pancreatitis and the large number of drugs that have been suggested as a potential cause of acute pancreatitis prompted us to use the case-control design in the EDIP study. The case-control design allowed us to study multiple drug exposures for a relatively rare disease such as acute pancreatitis. However, the case-control design is not very efficient for studying adverse reactions to drugs that are infrequently used. Many case-reports confirmed a causal association between azathioprine and acute pancreatitis by prompt relapse after controlled rechallenge.(12) Since exposure to azathioprine is low in the general population, we were unable to quantify the risk of acute pancreatitis associated with use of azathioprine in our international case-control study.

### **Pathogenesis and incidence of drug-induced acute pancreatitis**

The pathogenesis of drug-induced acute pancreatitis is incompletely understood. Drugs or drug metabolites may theoretically have a direct toxic effect on the pancreas. Among the NSAIDs, sulindac seems to stand out in its ability to induce pancreatitis. The delay between start of sulindac and development of symptoms is several weeks to months, and after rechallenge symptoms re-appear within weeks. This is compatible with a toxic effect on the pancreas. Didanosine-associated acute pancreatitis usually develops 10-18 weeks after start of therapy, which is well compatible with didanosine-induced mitochondrial toxicity.(13) ACE-inhibitors may predispose to pancreatitis by diminished degradation of bradykinin and substance P. For other drugs, an immunoallergic idiosyncratic reaction is more likely. Time between start of treatment and development of acute pancreatitis is usually within a few weeks for mesalazine, azathioprine, methyldopa and sulphonamides. Rechallenge with these drugs usually

leads to prompt recurrence of symptoms in a dose-independent manner. Other drugs may indirectly lead to acute pancreatitis by inducing known risk factors. For instance, estrogens, ritonavir,  $\beta$ -blockers, and other drugs are known to induce hyperlipidemia in susceptible patients. Hypercalcemia may develop secondary to excessive vitamin D intake. Erythromycin, somatostatin, and codeine increase the pressure of the sphincter of Oddi and may thereby induce pancreatitis. Fibrate-induced cholelithiasis may be responsible for subsequent acute pancreatitis.

The incidence of drug-induced pancreatitis is unknown. Reports to adverse reaction monitoring centers seem to indicate a low incidence of drug-induced pancreatitis, but as already mentioned, due to underreporting incidence rates cannot be validly estimated from spontaneous reporting schemes.(14-16) In clinical studies, 1-2% of acute pancreatitis is attributed to drugs.(9,17,18) This may be an underestimation, as drugs are often not recognized as a potential cause of acute pancreatitis.

## **DRUG-INDUCED ACUTE PANCREATITIS IN PERSPECTIVE**

In this thesis, we studied drug-induced acute pancreatitis with different pharmaco-epidemiological methods. Spontaneous reporting systems are an excellent tool to generate signals and hypotheses on new associations between drugs and acute pancreatitis. We showed, however, that these systems cannot be used to draw inferences on individual causal relationships between drugs and acute pancreatitis. The common view is that this also applies to case-reports described in the medical literature. However, in particular circumstances it is possible to assess the causal relationship between acute pancreatitis and an individual drug, based on information provided in case-reports. The detailed description of multiple patients who experienced a relapse of acute pancreatitis after controlled re-exposure to for instance mesalazine, azathioprine, or ACE-inhibitors proves that a definite causal relationship exists between these drugs and acute pancreatitis.

Guided by our studies on spontaneous reports and our review of the literature, we were able to quantify the association between five commonly used drug classes and acute pancreatitis. For many other drugs, exposure was too low to estimate the risk of acute pancreatitis. This means that future research on drug-induced acute pancreatitis should decide between an even larger field case-control study to increase the chance of detecting rare drug exposures as a cause, and initiating such studies in large databases such as the GPRD knowing that control of confounding will be difficult to achieve. Possibly, there is no real gain in performing such large studies if the expected incidence of a certain drug-pancreatitis association is low. Then, it may be better to rely on well-described individual case-histories.

This thesis shows that although some drugs are associated with acute pancreati-

tis, the clinical impact of drug-induced acute pancreatitis in the general population is modest. Of course, this tells little about the personal suffering of individuals who develop this potentially life-threatening adverse reaction. Because of the low incidence, we should rely on spontaneous reporting systems and case-reports in the medical literature to provide signals on new associations between drugs and acute pancreatitis. For associations that seem to be relatively frequent, a study in special patient groups might be initiated. For instance, a case-control study on azathioprine-associated pancreatitis could be nested in a cohort of patients with inflammatory bowel disease.

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Summary

5.2



The objective of this thesis was to estimate the incidence and mortality of acute pancreatitis and to study drugs as potential risk factors for acute pancreatitis. We started our exploration of drug-induced acute pancreatitis by studying reports of drug-induced acute pancreatitis notified to spontaneous reporting centres. After a literature review, we quantified the risk of acute pancreatitis associated with five different drug classes.

Chapter **1** provides a brief overview of acute pancreatitis and its aetiology, diagnosis, treatment and pathogenesis.

The incidence and mortality of acute pancreatitis between 1985 and 1995 was described in chapter **2.1**. In this period, there were over 22,000 admissions for acute pancreatitis in the Netherlands. Of the nearly 10,000 patients with a first attack of acute pancreatitis between 1985 and 1990, 11% experienced a relapse within 5 years and 6% developed chronic pancreatitis. The overall incidence of acute pancreatitis rose from 12.4 per 100,000 person-years in 1985 to 15.9/100,000 person-years in 1995. The incidence of acute pancreatitis rose in men as well as in women and increased markedly with age. The incidence of acute pancreatitis was low in children but increased with age to approximately 20 per 100,000 person-years at the age of 50 and to approximately 50 per 100,000 person-years in patients aged 80 years and over. The observed increase in the incidence of acute pancreatitis could not be explained by an increasing proportion of elderly in the population since the incidence standardised for age and gender increased from 12.4 per 100,000 person-years in 1985 to 14.8 per 100,000 in 1995. The overall annual mortality rates for acute pancreatitis remained fairly stable at 1.5/100,000 person-years between 1985 and 1995. The mortality was very low in children and young adults, but increased rapidly after 30 years of age to 14.4/100,000 person-years in patients aged 85 years and over. The case-fatality of first admissions declined from 14.3% in 1985 to 10.7% in 1995, but remained stable at approximately 3.2% for relapses of acute pancreatitis. The case-fatality increased rapidly with age up to approximately 35% in patients aged 85 years and over.

In studies based on hospital data, the incidence of acute pancreatitis may be underestimated if not all patients with acute pancreatitis are admitted to hospital. Chapter **2.2** describes a study on the incidence of acute pancreatitis in the general population. This study was performed in the Integrated Primary Care Information project, a general practitioner's database in the Netherlands. The total study population comprised 242,451 individuals who contributed a total of 599,368 person-years of experience to the study. There were 84 patients with a first attack of acute pancreatitis. Biliary pancreatitis was more frequent in women than in men (46% vs. 35%) while alcohol-related pancreatitis was more frequent in men than in women (29% vs. 3%). Five patients died during their first attack of acute pancreatitis. Two patients with definite pancreatitis were not referred to hospital. The incidence rate - standardised for age

and gender structure of the Dutch population in 1995 - was 14.2/100,000 person-years, which was close to the incidence of a first attack of acute pancreatitis in the study described in chapter 2.1 (13.7 per 100,000 person-years).

Chapter 3 consists of the description and evaluation of reports of drug-induced acute pancreatitis notified to drug monitoring centres and of reports of drug-induced acute pancreatitis described in the medical literature.

In chapter 3.1 we studied all reports of drug-induced acute pancreatitis notified to the Netherlands Center for Monitoring of Adverse Reactions to Drugs and the Netherlands Pharmacovigilance Foundation LAREB between January 1st 1977 and January 1st 1998. In total, 55 reports were notified to these drug monitoring centres. We obtained additional clinical information from the original reporters for all reports. The reports were reviewed, as to the probability of the diagnosis of acute pancreatitis, and the likelihood of a causal relationship with the suspected drug. Eleven reports were excluded, as we could not confirm the diagnosis of acute pancreatitis. In another ten reports, the causal relationship between the suspected drug and acute pancreatitis was considered unlikely. In the remaining 34 case-histories, the causal relationship with the suspected drug was considered definite in nine, probable in ten, and possible in 15 cases. Based on our algorithm, azathioprine, cimetidine, interferon- $\alpha$ , methyl dopa, metronidazole, olsalazine, and oxyphenbutazon had a definite causal relationship with acute pancreatitis. The association between interferon- $\alpha$  and acute pancreatitis was described in more detail in chapter 3.2. To summarize current knowledge, we performed an extensive literature search on drug-induced acute pancreatitis and its associated terms (Chapter 3.3). All English, German, French, and Dutch papers on drug-induced acute pancreatitis were retrieved. The causal relationship between drugs and acute pancreatitis was assessed according to a pre-specified algorithm that took into account the time relationship between drug exposure and development of acute pancreatitis, the absence or presence of other risk factors for acute pancreatitis, whether or not a rechallenge was performed, and the number of patients described. In total, over 150 drugs and drug classes have been associated with acute pancreatitis. According to our algorithm, 14 drugs or drug classes had a definite causal relation with acute pancreatitis: ACE-inhibitors, 5-ASA, asparaginase, azathioprine, codeine, didanosine, isoniazid, metronidazole, estrogens, pentavalent antimonials, beta-blockers, sulindac, tetracycline, and valproic acid.

Chapter 4 deals with the quantification of the association between acute pancreatitis and five different drug classes. We estimated the risk of acute pancreatitis associated with use of anti-ulcer drugs in the General Practice Research Database (GPRD) in chapter 4.1. The GPRD is a general practitioners database with medical data on more than four million inhabitants of the United Kingdom. To diminish potential confound-

ing by indication and protopathic bias, we selected all patients who received at least one prescription for an anti-ulcer drug in the period 1992-1997. The total study cohort consisted of 180,178 patients who received a total of 1,545,921 prescriptions for anti-ulcer drugs. In this cohort, there were only 36 patients with an idiopathic first episode of acute pancreatitis. The overall incidence rate of idiopathic acute pancreatitis during current use of acid-suppressing drugs was 9.9 per 100,000 person years (PY), 7.6 per 100,000 PY for past users, and 4.4 per 100,000 PY for non-users. After adjustment for age, gender and calendar year the RR was 1.6 for current use and 1.6 for past use of an acid-suppressing drug. A nested case-control analysis did not show an apparent duration or dose response relationship.

To further explore the association between drugs and acute pancreatitis, a multi-centre case-control study was initiated: the European study on drug-induced acute pancreatitis (EDIP). This study was performed simultaneously in Denmark, Italy, the Netherlands, Portugal, Sweden, and the United Kingdom. In the studies described in this thesis, drug use in patients with acute pancreatitis aged 50 to 85 years was compared to community controls. In these studies, data from Portugal and the United Kingdom was not used since in these countries no community controls were enrolled. Among the final 724 cases, 658 were admitted for a first attack of acute pancreatitis. Three hundred patients had evidence of gallstones and 88 patients had a history of alcohol abuse or used 5 units or more per day. A total of 1791 community controls were matched to the 724 cases. A high number of hospitalisations, smoking, high intake of alcohol, and a history of biliary disease, hyperlipidemia, peptic ulcer disease, pancreatic disease, and diabetes mellitus were all positively associated with development of acute pancreatitis.

Both spontaneous reports and case-reports suggest an association between ACE-inhibitors and acute pancreatitis, some with documented relapse after rechallenge to these agents. We assessed the risk of acute pancreatitis associated with these agents in Chapter 4.2. A higher proportion of patients with acute pancreatitis had used ACE-inhibitors than controls. Use of an ACE-inhibitor increased the risk of acute pancreatitis with 60%. Although the relative risk estimates varied slightly between individual ACE inhibitors, the confidence intervals overlapped. The risk of acute pancreatitis was higher during the first 6 months of therapy (OR 3.3) than in subsequent years (OR 1.4). There was a positive dose-effect relationship between the daily dose of ACE inhibitors and acute pancreatitis: OR 1.2 for < 1 DDD, 1.8 for 1-2 DDD, and 3.5 for > 2 DDD. The risk of acute pancreatitis associated with the use of ACE-inhibitors was higher in patients without biliary diseases: 2.7. Use of angiotensin receptor blockers was not associated with an elevated risk of acute pancreatitis (OR 0.9). Use of calcium channel blockers was also significantly associated with acute pancreatitis (OR 1.5). Two small case-control studies suggested a causal relationship between diuretics and acute pancreatitis. Our study could not substantiate this: neither loop diuretics, nor thiazide

diuretics were associated with an increased risk of acute pancreatitis.

Chapter **4.3** deals with the risk of acute pancreatitis associated with use of different psychotropic drugs. Use of tricyclic antidepressants, serotonin reuptake inhibitors, and benzodiazepines all showed a modest, non-significantly increased risk of acute pancreatitis. Short- and long acting benzodiazepines had similar risk estimates for acute pancreatitis. Use of antipsychotic drugs showed an adjusted odds ratio of 3.0. The risk of acute pancreatitis associated with antipsychotics was higher in patients aged 60-85 years (OR 4.1), than in younger patients (OR 1.3).

The risk of acute pancreatitis associated with use of lipid lowering drugs is described in chapter **4.4**. Use of fibrates was associated with an increased risk of acute pancreatitis with an OR of 3.5. The risk of acute pancreatitis during use of fibrates seemed higher in patients aged 60 years and over with an OR of 5.4, and in users of bezafibrate with an OR of 15.2. Use of HMG-CoA-reductase inhibitors was not associated with an increased risk of acute pancreatitis. In a subsequent study, the association between intake of vitamin D and acute pancreatitis was investigated. Use of vitamin D in the week prior to the index date was associated with an increased risk of acute pancreatitis with an : adjusted OR of 3.5. The risk of vitamin D associated acute pancreatitis seemed higher in patients without biliary pancreatitis: OR (24.7), in patients aged 40-60 years: OR 10.3, and in users of hydroxylated vitamin D: OR 13.9.

In the general discussion (chapter **5**), the findings of the studies in this thesis are discussed against the background of drug safety aspects, strengths and limitations of our studies, and future perspectives of studies on drug-induced acute pancreatitis.

Samenvatting

5.3



Dit proefschrift handelt over de associatie tussen het gebruik van geneesmiddelen en het ontstaan van acute pancreatitis. De in dit proefschrift beschreven onderzoeken werden uitgevoerd naar aanleiding van meldingen van aan geneesmiddelen toegeschreven acute pancreatitis, die werden ontvangen door de Sectie Geneesmiddelenbewaking van de Inspectie voor de Gezondheidszorg. Na een beschrijving van deze meldingen en een uitgebreid literatuuronderzoek werd het risico bestudeerd op het ontstaan van acute pancreatitis na het gebruik van geneesmiddelen uit vijf verschillende groepen.

Hoofdstuk 1 geeft een overzicht van de oorzaken, diagnose, behandeling en pathogenese van acute pancreatitis.

De incidentie en mortaliteit van acute pancreatitis tussen 1985 en 1995 werd beschreven in hoofdstuk 2.1. Gedurende deze 10-jaars periode werden er circa 22.000 opnames in Nederland toegeschreven aan acute pancreatitis. Van de bijna 10.000 patiënten met een eerste aanval van acute pancreatitis kreeg 11% een recidief in de eerste vijf jaar en 6% ontwikkelde chronische pancreatitis. De incidentie van acute pancreatitis steeg van 12,4 naar 15,9 gevallen per 100.000 persoonsjaren. Deze stijging was zichtbaar bij zowel mannen als vrouwen. De incidentie van acute pancreatitis nam sterk toe met opklimmende leeftijd. Op de kinderleeftijd was de incidentie zeer laag maar de incidentie steeg tot 50 per 100.000 persoonsjaren op tachtigjarige leeftijd. De stijgende incidentie van acute pancreatitis kon niet worden verklaard door een vergrijzende populatie daar de voor leeftijd en geslacht gecorrigeerde incidentie eveneens steeg tussen 1985 en 1995 (van 12,4 naar 14,8 per 100.000 persoonsjaren). De mortaliteit van acute pancreatitis bleef stabiel op 1,5 per 100.000 persoonsjaren. De mortaliteit was laag bij kinderen, maar steeg snel na het 30e levensjaar tot 14,4 per 100.000 persoonsjaren op 85-jarige leeftijd. Ook de letaliteit steeg snel met toenemende leeftijd tot 35% op 85 jarige leeftijd. De letaliteit van patiënten met een eerste aanval van acute pancreatitis daalde van 14,3% in 1985 naar 10,7% in 1995. De letaliteit van patiënten met een recidief van acute pancreatitis bleef gelijk op 3,2%. De hierboven beschreven studie was gebaseerd op ontslaggegevens van ziekenhuizen. Incidentiestudies die gebaseerd zijn op ontslaggegevens kunnen de werkelijke incidentie onderschatten wanneer niet alle patiënten naar het ziekenhuis worden verwezen. In hoofdstuk 2.2 wordt een studie beschreven naar de incidentie van acute pancreatitis welke werd uitgevoerd in een huisartsendatabestand: de 'Integrated Primary Care Information project' (IPCI). Dit betreft geautomatiseerde huisartsengegevens van een populatie van ongeveer 300.000 personen. Middels dit databestand konden we bepalen welk percentage van de patiënten met acute pancreatitis werd verwezen naar het ziekenhuis. De totale studiep populatie betrof 242.451 personen met een totale 'follow-up' tijd van 599.368 persoonsjaren. Er waren 84 patiënten met een eerste aanval van acute pancreatitis. Acute pancreatitis door galstenen was frequenter

bij vrouwen dan bij mannen (46 vs. 35%). Acute pancreatitis bij gebruik van alcohol was daarentegen frequenter bij mannen (29 vs. 3%). Vijf patiënten overleden aan de aanval van acute pancreatitis. Slechts twee patiënten werden niet naar het ziekenhuis verwezen. De voor leeftijd en geslacht gecorrigeerde incidentie bedroeg 14,2 per 100.000 persoonsjaren, hetgeen overeen kwam met de incidentie die werd beschreven in hoofdstuk 2.1.

Hoofdstuk 3.1 beschrijft alle meldingen in de periode 1977-1998 van aan geneesmiddelen toegeschreven acute pancreatitis van de Sectie Geneesmiddelenbewaking van de Inspectie voor de Gezondheidszorg en de stichting LAREB. Gedurende deze jaren waren er in totaal 55 meldingen van acute pancreatitis. Om de diagnose acute pancreatitis en de causale relatie tussen gebruik van het geneesmiddel en het ontstaan van acute pancreatitis te valideren werd aanvullende klinische informatie opgevraagd bij de oorspronkelijke melders. In 11 meldingen kon de diagnose acute pancreatitis niet worden bevestigd. In 10 andere meldingen was de causale relatie tussen het gebruik van het verdachte geneesmiddel en het ontstaan van acute pancreatitis onwaarschijnlijk. In negen meldingen was de causale relatie zeker. Het betrof de geneesmiddelen azathioprine, cimetidine, interferon- $\alpha$ , methyldopa, metronidazole, olsalazine en oxyphenbutazon. De causale relatie was waarschijnlijk in 10 andere meldingen en mogelijk in de 15 overgebleven meldingen. De associatie tussen het gebruik van interferon- $\alpha$  en het ontstaan van acute pancreatitis werd in meer detail in hoofdstuk 3.2 beschreven. Hoofdstuk 3.3 geeft een literatuuroverzicht over acute pancreatitis door geneesmiddelen. Alle Engels-, Duits-, Frans- en Nederlandstalige artikelen over aan geneesmiddelen toegeschreven acute pancreatitis werden beoordeeld op hun causaliteit volgens een vooraf gedefinieerd beslismodel. Meer dan 150 geneesmiddelen en geneesmiddelgroepen werden met het ontstaan van acute pancreatitis in verband gebracht. Op basis van het beslismodel hadden 14 geneesmiddelen een zekere causale relatie met het ontstaan van acute pancreatitis. Het betrof ACE-remmers, 5-ASA, asparaginase, azathioprine, codeïne, didanosine, isoniazide, metronidazole, oestrogenen, pentavalente antimonials, beta-blokkers, sulindac, tetracycline en valproïnezuur.

In hoofdstuk 4 wordt de associatie tussen vijf verschillende geneesmiddelengroepen en acute pancreatitis gekwantificeerd. De associatie tussen het gebruik van maagzuurremmende middelen en acute pancreatitis werd onderzocht in de General Practice Research Database (GPRD). De GPRD is een geautomatiseerd huisartsenbestand met de medische gegevens van vier miljoen inwoners van het Verenigd Koninkrijk. Om de invloed van 'confounding by indication' en 'protopathic bias' te verminderen, selecteerden we alle patiënten die tussen 1992-1997 tenminste één prescriptie van een maagzuurremmer kregen. Het studiecohort bestond uit 180.178 patiënten, die in totaal 1.545.921 prescripties ontvingen voor maagzuurremmer. In dit cohort ontwikkelden

36 personen een eerste idiopathische aanval van acute pancreatitis. De incidentie bedroeg 9,9 per 100.000 persoonsjaren gedurende het gebruik van zuurremmers en 4,4 per 100.000 persoonsjaren voor personen die nooit zuurremmers hadden gebruikt. Hoewel de incidentie hoger leek was dit niet statistisch significant: RR 1.6 (95% BI: 0.6-4.2). Een genest patiënt-controle onderzoek liet geen duur- of dosisrelatie zien.

Om de relatie tussen geneesmiddelen en acute pancreatitis verder te onderzoeken werd een internationaal patiënt-controle onderzoek verricht: de 'European study on drug-induced acute pancreatitis (EDIP)'. Deze studie werd verricht in Denemarken, Italië, Nederland, Portugal, Zweden en het Verenigd Koninkrijk. Het gebruik van geneesmiddelen door patiënten met acute pancreatitis werd vergeleken met het geneesmiddelengebruik van aselekt getrokken controlepersonen uit de algemene populatie. De in dit proefschrift beschreven studies maken alleen gebruik van de verzamelde gegevens uit Denemarken, Italië, Nederland, Portugal, en Zweden, daar in de overige landen uitsluitend ziekenhuiscontroles werden verzameld. Van de uiteindelijke 724 patiënten met acute pancreatitis hadden 658 een eerste aanval. Bij driehonderd patiënten werden galstenen vastgesteld, bij 88 patiënten was sprake van een te hoog alcoholgebruik. In totaal werden 1791 controlepersonen vergeleken met de 724 patiënten met acute pancreatitis. Een hoog aantal ziekenhuisopnames, roken, alcoholmisbruik, en aanwezigheid van galwegziekten, hyperlipidemie, ulcus pepticum, pancreasziekten en diabetes mellitus in de voorgeschiedenis waren allen positief geassocieerd met acute pancreatitis.

In de literatuur is meermalen een associatie gesuggereerd tussen het gebruik van ACE-remmers en het ontstaan van acute pancreatitis. In hoofdstuk **4.2** onderzochten we deze relatie in de EDIP studie. Het gebruik van ACE-remmers in de week voorafgaand aan opname was geassocieerd met een verhoogd risico op het verkrijgen van acute pancreatitis: OR 1.6 (95% BI:1.1-2.3). Het risico op acute pancreatitis was het hoogst gedurende de eerste zes maanden van ACE-remmer therapie en nam toe bij het gebruik van een hogere dosis. Het met ACE-remmers geassocieerde risico op acute pancreatitis was iets hoger bij patiënten die geen galstenen hadden: OR 2.7 (95% BI: 1.3-5.8). Het gebruik van ATII receptor blokkers verhoogde het risico op acute pancreatitis niet. Twee kleine patiënt-controle onderzoeken die werden uitgevoerd in de jaren zeventig suggereerden een verband tussen het gebruik van diuretica en acute pancreatitis. In deze studie kon geen verband worden aangetoond tussen acute pancreatitis en het gebruik van thiazide- of lisdiuretica. Wel leek er een verband te zijn tussen het gebruik van kaliumsparende diuretica en acute pancreatitis.

Hoofdstuk **4.3** beschrijft een studie waarbij de relatie tussen het gebruik van psychotrope middelen en het ontstaan van acute pancreatitis werd onderzocht. Gebruik van tricyclische antidepressiva, serotonine re-uptake inhibitors en benzodiazepines hadden allen een klein en niet-significant verhoogd risico op acute pancreatitis. Gebruik van antipsychotica daarentegen verhoogde het risico op acute pancreatitis

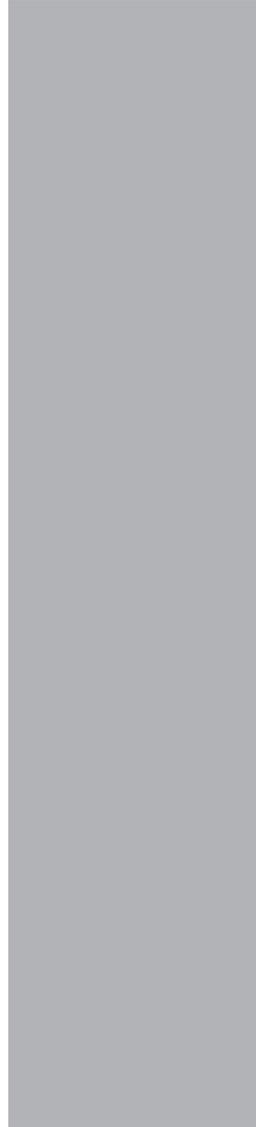
met een factor 3. Dit verhoogde risico leek meer uitgesproken bij oudere patiënten (OR 4.1).

Het verband tussen het gebruik van lipideverlagende geneesmiddelen en het optreden van acute pancreatitis wordt beschreven in hoofdstuk **4.4**. Fibraten waren geassocieerd met een verhoogd risico op acute pancreatitis met een OR van 3.5. Het risico op acute pancreatitis tijdens het gebruik van fibraten leek hoger bij ouderen (OR 5.4), en bij gebruikers van bezafibrate (OR 15.2). Gebruik van HMG-CoA-reductase remmers was niet geassocieerd met een verhoogd risico op acute pancreatitis.

In hoofdstuk **4.5** onderzochten we de relatie tussen het gebruik van vitamine D en het ontstaan van acute pancreatitis. Gebruik van vitamine D was geassocieerd met een verhoogd risico op acute pancreatitis met een OR van 3.5. Het risico van aan vitamine D toegeschreven acute pancreatitis leek relatief hoog bij oudere patiënten met een OR van 10.3, en bij gebruikers van gehydroxyleerd vitamine D met een OR van 13.9.

In hoofdstuk **5** worden de studies samengevat en worden de verschillende methodologische aspecten besproken. Voorts wordt in dit hoofdstuk het onderwerp acute pancreatitis door geneesmiddelen in perspectief geplaatst.

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Ingo Eland was born on July 10th 1970 in Rotterdam. He attended secondary school at the Titus Brandsma College in Dordrecht where he graduated cum laude in 1988. In that same year he started his medical training at the Erasmus University Rotterdam. He obtained his medical degree in 1996 cum laude. In 1996 he started his research project described in this thesis at the department of Internal Medicine of the Erasmus MC (promotors prof. dr. B.H.Ch. Stricker, prof. J.H.P. Wilson). In September 2000, he started his training in Internal Medicine at the department of Internal Medicine of the Erasmus MC in Rotterdam (chair prof. dr. H.A.P. Pols). The author is married to Iris Martha. They have two children named Sanne and Timo.