Acute pancreatitis: from treatment to prevention

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FROM TREATMENT TO PREVENTION

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ACUTE PANCREATITIS – FROM TREATMENT TO PREVENTION
Academic thesis, University of Leiden, The Netherlands

ISBN: 978-94-6510-178-1
Lay-out and printing: www.proefschriftmaken.nl

Printing of this thesis was financially supported by ABN AMRO, Chipsoft, Nederlandse Vereniging voor Gastroenterologie, Pancreatitis Werkgroep Nederland, Prion Medical, SBOH, St. Antonius Ziekenhuis, and Universiteitsbibliotheek Leiden.

ACUTE PANCREATITIS

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Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof. dr. ir. H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op donderdag 17 oktober 2024
klokke 16.00 uur

door

Noor Josien Sissingh
geboren te Assen
in 1993

PROMOTIECOMMISSIE

Promotor:	Prof. dr. J.E. van Hooft
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Leescommissie:	Prof. dr. B. van Hoek Prof. dr. S.C. Cannegieter Prof. dr. F.P. Vleggaar (Universitair Medisch Centrum Utrecht) Dr. B.A. Bonsing Dr. R.B. Takkenberg (Amsterdam Universitair Medisch Centra)

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CHAPTER 1

General introduction and thesis outline

GENERAL INTRODUCTION

In 1652, the Dutch anatomist Nicolaes Tulp initiated the exploration of acute pancreatitis by presenting its first official description as an inflammatory pancreatic disorder (1). Over 370 years later, acute pancreatitis has evolved into the most prevalent gastrointestinal disease leading to acute hospitalization (2), with its incidence continuing to rise (3). An evident illustration of this trend can be seen in the Netherlands, where hospital admissions for acute pancreatitis have witnessed a fourfold increase in the past 25 years (4, 5). This rise, potentially associated with increased lifestyle-related risk factors linked to the development of acute pancreatitis (6, 7), not only reflects its impact on patients but also the broader socioeconomic consequences. Today, in high-income countries, the most common etiologies are biliary disease and excessive alcohol consumption (8, 9). However, a variety of additional etiologies have also been acknowledged (10). Each of these etiologies involves distinct pathophysiological pathways (11, 12). Nonetheless, the ultimate common trigger is thought to be the premature activation of pancreatic enzymes, resulting in local tissue injury and inflammatory responses (13). Following the onset, patients experience severe upper abdominal pain, which leads to hospitalization where treatment is initiated (14).

The current treatment goals for acute pancreatitis are twofold (10). The first goal of treatment is to achieve symptom relief and address complications. Early treatment is restricted to supportive care and involves analgesics and fluid resuscitation, after which most patients recover within several days (15-17). In 20% of patients, the disease follows a more severe course with pancreatic and peripancreatic necrosis being the main determinant (16, 18). Secondary infection of this necrosis stands out as the most alarming complication, leading to extended hospital stays and significant morbidity and mortality (19). The second treatment goal is to prevent the recurrence of acute pancreatitis (10). Pancreatitis recurrence exposes patients to additional episodes of potential complications and increases the risk of developing chronic pancreatitis (20). A crucial aspect is the accurate detection of the underlying etiology, as each requires a different treatment approach. The guidelines recommend performing a cholecystectomy in patients with a biliary etiology and providing alcohol cessation support for patients with excessive alcohol consumption (10, 21, 22).

Since Tulp's discovery, the management of acute pancreatitis has seen significant improvements. Numerous studies, particularly focusing on infected necrotizing pancreatitis and acute biliary pancreatitis, have been conducted, wherein the Netherlands has maintained its pioneering role, mostly due to the unwavering commitment of the Dutch Pancreatitis Study Group (21, 23-26). Yet, many questions '*from treatment to prevention*' remain unanswered in current clinical practice. In this thesis, I address

several gaps in the existing literature with the aim to improve outcomes of patients with acute pancreatitis.

THESIS OUTLINE

In the first part of this thesis, I focus on the optimal timing of minimally invasive interventions for infected necrotizing pancreatitis. The second part directs the spotlight towards a less frequently discussed complication known as splanchnic vein thrombosis, and explores the evidence supporting the use of anticoagulant therapy as part of its treatment. In the third part, I concentrate on strategies for preventing recurrence after the initial episode of acute pancreatitis.

PART I – TREATMENT OF INFECTED NECROTIZING PANCREATITIS

Infected necrosis develops in approximately one-third of patients with necrotizing pancreatitis (16). This condition is believed to result from the translocation of intestinal bacteria across the gut mucosa (27). While there have been attempts to prevent secondary infection using prophylactic systemic antibiotics or enteral probiotics, no beneficial effect has been proven, making such interventions not recommended (28, 29). However, if the diagnosis is confirmed through imaging or microbiological culture, or if there is suspicion based on clinical deterioration, intravenous broad-spectrum antibiotics should be initiated (10, 30), with a pancreatic intervention often taking place thereafter (16, 31, 32). Until the 2010 publication of the PANTER trial, open surgical necrosectomy was the standard initial intervention (23). This trial demonstrated the superiority of a minimally invasive surgical 'step-up' approach – involving percutaneous catheter drainage and, when necessary, laparoscopic necrosectomy – over the traditional open method. Following advancements in endoscopic techniques, the 2018 TENSION trial compared the endoscopic step-up approach, comprising endoscopic transluminal drainage followed by endoscopic necrosectomy, to the surgical step-up approach (24). The results favored the endoscopic group, showing shorter hospital stays and fewer pancreaticocutaneous fistulas. Consequently, the endoscopic step-up approach is now considered the best practice for patients with endoscopically accessible infected necrotic collections (33). Another important topic in the treatment of infected necrotizing pancreatitis is determining the best timing for initiating catheter drainage. This was explored in the recent POINTER trial conducted by the Dutch Pancreatitis Study Group (26). In this multicenter trial, 104 patients with infected necrotizing pancreatitis were randomly assigned to immediate drainage

following diagnosis or postponed drainage until the stage of walled-off necrosis. The results showed no differences in mortality and complication rates. However, among patients treated with the postponed drainage approach, fewer interventions were needed, and more than a third did not undergo any drainage procedure throughout a 6-month follow-up. Yet, the long-term advantages of this approach remain unknown. It is hypothesized that infected necrotic collections, when treated conservatively with only antibiotics, could lead to persistent or long-term complications that require interventions during extended follow-ups. Therefore, in **Chapter 2**, the POINTER trial's long-term follow-up is described. This study compares the long-term clinical outcomes of patients with infected necrotizing pancreatitis who underwent either an immediate or postponed drainage approach.

PART II – SPLANCHNIC VEIN THROMBOSIS IN ACUTE PANCREATITIS

The splanchnic venous system drains the gastrointestinal organs and consists of the portal vein, splenic vein, and superior mesenteric vein (34). Due to their proximity to the pancreas, these veins are susceptible to complications during episodes of acute pancreatitis, especially in cases of necrotizing pancreatitis (35). Splanchnic vein thrombosis is a vascular complication found in 2% to 51% of acute pancreatitis patients, primarily influenced by the severity of the disease (36-38). This thrombosis can manifest as an intraluminal filling defect on contrast-enhanced computed tomography (39). The development of splanchnic vein thrombosis in acute (necrotizing) pancreatitis is attributed to several mechanisms (34, 40), all of which align with the principles of Virchow's Triad (41). Firstly, pancreatic edema and inflammation may result in venous stasis. Additionally, the presence of pancreatic or peripancreatic collections can further contribute to this stasis. Secondly, acute pancreatitis can initiate a systemic inflammatory response, the extent of which typically parallels disease severity, leading to hypercoagulability. Lastly, both necrotic tissue and the release of activated pancreatic enzymes may directly damage vascular endothelial cells.

A primary challenge with this vascular complication is the lack of standardized treatment guidelines tailored for acute pancreatitis (10). Available guidelines advocating therapeutic anticoagulants use lean heavily on studies focused on patients with persistent thrombotic risk (42-45). This contrasts with the transient inflammatory nature of acute pancreatitis, raising questions about the efficacy of anticoagulant therapy in these patients. In **Chapter 3**, a systematic review and meta-analysis of all available evidence to assess whether therapeutic anticoagulants improve clinical outcomes in patients with acute pancreatitis and splanchnic vein thrombosis is presented.

Without evidence-based recommendations, clinicians often rely on their own judgement for treatment decisions. To date, the collective opinion of pancreatologists on therapeutic anticoagulation remains unknown. One notable concern in clinical settings is the risk of bleeding. Necrotizing pancreatitis can directly erode blood vessels, leading to pseudoaneurysm formation (46). Furthermore, complications such as infected necrosis frequently demand invasive interventions, further increasing the risk of bleeding (47). **Chapter 4** describes a survey and case-vignette study among Dutch pancreatologists to evaluate their current perspectives on using therapeutic anticoagulants for splanchnic vein thrombosis in acute pancreatitis.

Similar to anticoagulant therapy, there is limited knowledge about the natural progression of splanchnic vein thrombosis in acute pancreatitis and its associated complications. While some believe that its course is primarily driven by the pancreatitis itself, this condition can lead to severe complications, such as hypertensive bleeding and small bowel ischemia (48, 49). Gaining insight into this is vital, as it might influence treatment decisions. Most prior studies were of limited scale and lacked a comparative group without thrombosis (46, 50-52). **Chapter 5** summarizes the full clinical impact of splanchnic vein thrombosis, utilizing a large, observational, multicenter cohort study of patients with necrotizing pancreatitis.

PART III – PREVENTION OF RECURRENT ACUTE PANCREATITIS

Embracing the age-old saying that 'Prevention is better than cure,' the focus shifted from treatments to preventive strategies for disease progression. Over the years, the paradigm that acute, recurrent, and chronic pancreatitis are separate disease entities has evolved into the concept of a disease continuum. Some patients with acute pancreatitis will develop chronic pancreatitis, often encountering recurrent episodes of acute pancreatitis in between (53-55). Moreover, patients with chronic pancreatitis may even progress to pancreatic cancer (56, 57). Whether acute pancreatitis is associated with pancreatic cancer is a matter of continued debate (58). **Chapter 6** begins by examining statistics and risk factors that influence disease progression in an observational long-term follow-up cohort study.

As previously mentioned, guided preventive treatments depend on the accurate diagnosis of the underlying etiology (10). Imaging techniques such as (endoscopic) ultrasound and magnetic resonance cholangiopancreatography are currently used to assess the biliary system for gallstones (59, 60). In daily practice, gallstones identified through these imaging modalities might be overlooked or remain untreated in patients

with acute pancreatitis who consume excessive amounts of alcohol. This lack of action potentially increases the risk of pancreatitis recurrence and other biliary complications (21). In **Chapter 7**, an observational study from a prospective multicenter cohort is summarized. This study assesses the incidence and clinical relevance of gallstones in patients presumed to have acute alcoholic pancreatitis.

After diagnosing an alcoholic etiology, it is important to address alcohol consumption, the main preventable risk factor for recurrent episodes (53, 61). While prior research, varying in follow-up durations, reported recurrence rates between 24% and 46% (53, 62-64), these rates dropped close to zero with the achievement of alcohol cessation (62, 64). This underscores the urgency of attempts to reduce alcohol consumption. Although guidelines emphasize dedicated follow-up visits, they fall short of proposing a concrete treatment plan. **Chapter 8** introduces a nationwide survey aimed to assess current practices related to alcohol cessation support for patients with acute alcoholic pancreatitis, spotlighting potential areas for improvement.

A 2009 Finnish trial demonstrated encouraging outcomes from repeated motivational interventions compared to a single session for patients with acute alcoholic pancreatitis (22). However, the true effectiveness of this intervention may be overestimated, considering that participants in a traditional randomized trial were likely those potentially motivated to quit or reduce alcohol. Therefore, the multicenter cluster randomized PANDA trial is described in **Chapter 9**. This trial investigates whether implementation of a structured alcohol cessation support program, as compared to current practice, reduces the recurrence of pancreatitis in patients after their first episode of acute alcoholic pancreatitis.

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PART I

Treatment of infected necrotizing pancreatitis

CHAPTER 2

Long-term outcome of immediate versus postponed intervention in patients with infected necrotizing pancreatitis (POINTER): *multicenter randomized trial*

Annals of Surgery 2023

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ABSTRACT

Objective: To compare the long-term outcomes of immediate drainage versus the postponed-drainage approach in patients with infected necrotizing pancreatitis.

Background: In the randomized POINTER trial, patients assigned to the postponed-drainage approach using antibiotic treatment required fewer interventions, as compared with immediate drainage, and over a third were treated without any intervention.

Methods: Clinical data of those patients alive after the initial 6-month follow-up were re-evaluated. The primary outcome was a composite of death and major complications.

Results: Out of 104 patients, 88 were re-evaluated with a median follow-up of 51 months. After the initial 6-month follow-up, the primary outcome occurred in 7 of 47 patients (15%) in the immediate-drainage group and 7 of 41 patients (17%) in the postponed-drainage group (RR 0.87, 95% CI 0.33-2.28; p=0.78). Additional drainage procedures were performed in 7 patients (15%) versus 3 patients (7%) (RR 2.03; 95% CI 0.56-7.37; p=0.34). The median number of additional interventions was 0 (IQR 0-0) in both groups (p=0.028). In the total follow-up, the median number of interventions was higher in the immediate-drainage group than in the postponed-drainage group (4 vs 1, p=0.001). Eventually, 14 of 15 patients (93%) in the postponed-drainage group who were successfully treated in the initial 6-month follow-up with antibiotics and without any intervention, remained without intervention. At the end of follow-up, pancreatic function and quality of life were similar.

Conclusions: Also, during long-term follow-up, a postponed drainage approach using antibiotics in patients with infected necrotizing pancreatitis results in fewer interventions as compared with immediate drainage and should therefore be the preferred approach.

INTRODUCTION

Acute pancreatitis mostly runs a mild clinical course, but 20% of patients develop severe pancreatitis with necrosis (1-4). Secondary infection of pancreatic and peripancreatic necrosis puts these patients at risk of significant morbidity and 10% to 39% mortality (5). Several randomized studies have attempted to optimize the treatment of patients with infected necrotizing pancreatitis (6-11). Besides antibiotic treatment, the minimally invasive step-up approach, with catheter drainage of the infected necrotic collection as the first step followed by minimally invasive necrosectomy when needed, is the current standard treatment strategy. However, the optimal timing of drainage in infected necrotizing pancreatitis remains unknown and varies widely in current practice (12-14).

The recent multicenter randomized POINTER trial compared immediate catheter drainage within 24 hours after diagnosing infected pancreatic necrosis, with postponed catheter drainage (11). At 6-month follow-up, immediate drainage was not superior to postponed drainage regarding complications. In fact, the postponed-drainage approach significantly reduced the number of invasive interventions, both catheter drainage and necrosectomy. Some 19 patients (39%) assigned to the postponed-drainage group did not require any intervention because their clinical condition improved with antibiotic treatment only; 17 of these patients (35%) survived. The question remains whether these relative benefits of the postponed-drainage approach persist after the initial 6-month follow-up. Some have argued that infected (peri)pancreatic necrotic collections, which are initially treated conservatively with antibiotics could lead to persistent complications requiring intervention and ultimately causing mortality during longer follow-up.

Therefore, the current study evaluates new events beyond the initial 6-month follow-up on long-term clinical outcomes of patients enrolled in the POINTER trial.

METHODS

Study design

Between August 2015 and October 2019, a total of 104 patients with infected necrotizing pancreatitis were enrolled in the multicenter randomized POINTER (Postponed or Immediate Drainage of Infected Necrotizing Pancreatitis) trial (11, 15). The study was conducted in 22 Dutch hospitals collaborating with the Dutch Pancreatitis Study Group (DPSG). Infected necrosis was defined as either a positive fine-needle aspiration (FNA) culture, presence of gas in (peri)pancreatic necrosis on contrast-enhanced

computed tomography, and after 14 days of onset, clinical signs of infection were also considered to be diagnostic if other causes of infections were ruled out. Clinical signs of infection were defined as: persistent (multiple) organ failure, or the presence of 2 of 3 elevated inflammatory parameters (temperature >38.5, C-reactive protein levels or leukocyte count) for three consecutive days. Patients were randomly assigned to immediate catheter drainage (55 patients) or postponed catheter drainage (49 patients). The study protocol of the current investigator-initiated long-term follow-up study was approved by the institutional review board of the Amsterdam UMC. All authors had access to the study data, and reviewed and approved the final version of the manuscript. The study was conducted in accordance with the principles of the Declaration of Helsinki and reported according to the STROBE Checklist (Supplementary Table S1, Supplemental Digital Content 1, http://links.lww.com/ SLA/E733) (16).

Long-term follow-up protocol

Surviving patients from the POINTER trial were informed about the study by telephone and subsequently invited to participate. Written informed consent was obtained from all patients with the exception of deceased patients. Eligible patients were evaluated until June 2022, following the initial POINTER study which had a 6-month follow-up. Clinical data regarding death, complications, interventions (i.e. drainage and necrosectomy procedures), readmission and disease course was retrieved retrospectively from medical records. Interventional procedures related to disconnected pancreatic duct syndrome were also recorded. Additional data were collected by a telephone conversation with patients or family members by the study coordinators (C.v.V. and N.S.). The choice of treatment (i.e., type and timing of interventions) was left to the treating physician and no particular criteria were formulated to guide the decisions of the physicians. For data collection, online database software (Castor EDC, Amsterdam, the Netherlands) was used.

Outcomes

The primary outcome was a composite of death and major complications (i.e., new-onset (multiple) organ failure, bleeding requiring intervention, perforation of a visceral organ requiring intervention or enterocutaneous fistula, similar to other trials and follow-up studies performed by our group (6, 17). This primary outcome differed from the original primary outcome (i.e. Comprehensive Complication Index [CCI]), because CCI would be less relevant during follow-up, because this tool was developed to assess short-term complications (18-20). The primary outcome was selected based on the hypothesis that residual (peri)pancreatic necrotic collections, especially in the postponed treatment group, could require new interventions and ultimately cause mortality during longer follow-up. In accordance with the initial study, secondary outcomes included individual major complications, incisional hernia, pancreaticocutaenous fistula, wound infection,

interventions, the total length of intensive care and hospital stay related to pancreatitis length. In addition, the occurrence of recurrent acute pancreatitis and chronic pancreatitis was assessed. Furthermore, we evaluated exocrine and endocrine pancreatic function based on a questionnaire, and quality of life measured with the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36) (21). Outcomes were assessed for the period after the trial's initial 6-month follow-up until the end of long-term follow-up *('new events after the initial 6-month follow-up'*) for all patients who were still alive after the initial 6-month follow-up. Separately, all events between the time of randomization and the end of long-term follow-up ('*total follow-up')* were reported for all patients, including patients who died in the initial 6-month follow-up, with the exception of patients who declined to participate in this follow-up study. This will provide a complete overview and accurate comparison between the 2 different treatment groups.

Definitions

All definitions were according to the initial POINTER trial and are explained in detail in the Supplementary Table S2 (Supplemental Digital Content 1, http://links.lww.com/SLA/E733). Patients were considered to have endocrine pancreatic insufficiency in case of use of diabetes medication (i.e. oral medication or insulin therapy), not used at the time of randomization. Exocrine pancreatic insufficiency was defined as the use of pancreatic enzymes, not used at the time of randomization. We considered successful treatment with antibiotics only if patients survived the initial 6-month follow-up and were treated without any intervention during total follow-up. The diagnosis of disconnected duct was based either on radiological confirmation or on an amylase level in external drain fluid of 3 times the upper limit of normal amylase level The follow-up period was defined as the time between randomization and the date of data entry in surviving patients or the date of death in deceased patients.

Statistical analysis

The analysis was performed according to the intention-to-treat principle. Outcome measures are expressed as means ± standard deviation (SD) or as medians with interquartile ranges (IQR), depending on the distributional properties. Categorical data are presented as counts and proportions. For normally distributed continuous data, statistical significance was assessed using the Student's-*t*-test. For non-normally distributed continuous data, the Mann-Whitney U test was performed. For categorical data, the Fisher's exact test was performed. Sensitivity analyses excluding patients in whom the diagnosis was based on FNA and radiographic appearance were performed. Results are expressed as relative risks (RRs) with corresponding 95% confidence intervals (CI). All reported *P* values are two-sided, and a *P* value of less than 0.05 was considered statistically significant. *P* values were not adjusted for multiple testing. All statistical analyses were conducted with IBM Statistic SPSS 26.0.

RESULTS

Overall, 104 patients with infected necrotizing pancreatitis were randomized in the initial POINTER trial. As shown in Fig 1, 12 of 104 patients died during the initial 6-month follow-up; 7 patients in the immediate-drainage group versus 5 patients in the postponed-drainage group. Of the 92 surviving patients, 4 patients (who were all still alive) did not consent to participate in the current long-term follow-up study, leaving 88 patients (47 patients in the immediate-drainage group and 41 patients in the postponed-drainage group) to be included in the analysis 'new events after the initial 6-month follow-up'. These 88 patients, together with the 12 patients who died in the initial 6-month follow-up, were included in the 'total follow-up' analysis, resulting in a total of 100 patients (54 in the immediate-drainage group and 46 in the postponed-drainage group). At the end of the long-term follow-up, questionnaires were obtained from 79 patients (42 patients in the immediate-drainage group and 37 patients in the postponed-drainage group). Baseline characteristics were similar between the 2 groups (Supplementary Table S3, Supplemental Digital Content 1, http://links.lww.com/SLA/E733) (11). The total follow-up was 51 months (IQR 31) (50 months (IQR 32) in the immediate-drainage group and 51 months (IQR 29) in the postponed-drainage group), and did not statistically differ among groups (p=0·91).

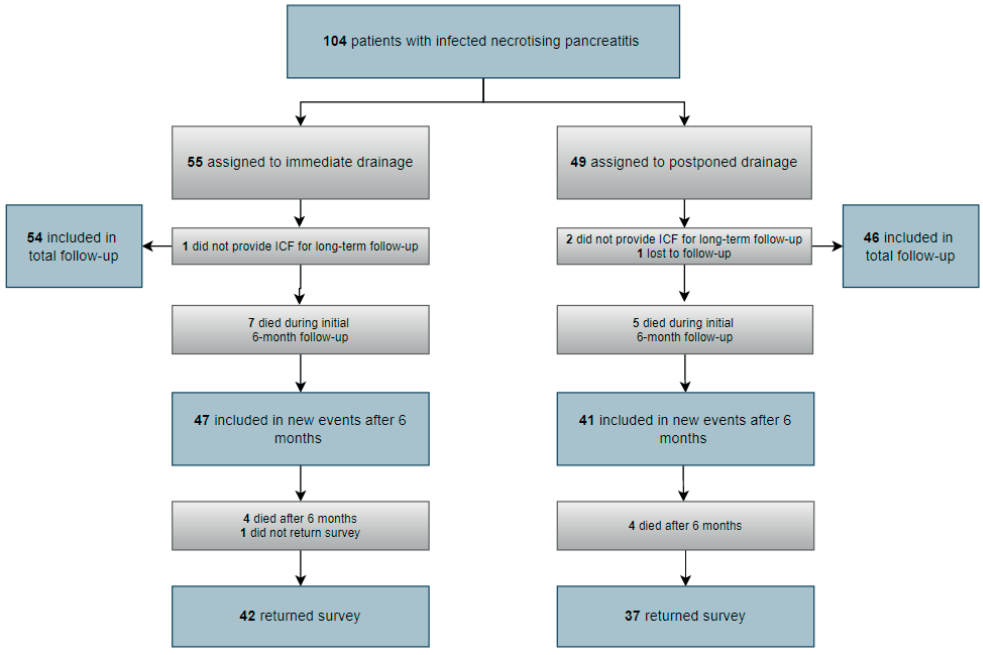

Figure 1. Trial profile

New events after the initial 6-month follow-up

After the initial 6-month follow-up, the composite primary outcome of death and major complications occurred in 7/47 patients (15%) in the immediate-drainage group and 7/41 patients (17%) in the postponed-drainage group (RR 0·87; 95% CI 0·33-2·28; p=0·78) (Table 1). Death occurred in 4 patients in the immediate-drainage group (9%) and in 4 patients in the postponed-drainage group (10%), (RR 0·87; 95% CI 0·23-3·27; p=1·00). Two deaths in the immediate-drainage group were directly related to pancreatitis, whereas none of the deaths in the postponed-drainage group (Supplementary Table S4, Supplemental Digital Content 1, http://links.lww.com/SLA/E733). No significant differences were found in the individual components of major complications, including new-onset organ failure (9% in the immediate-drainage group and 5% in the postponed-drainage group; RR 1·75; 95% CI 0·34-9·04; p=0·68), multiple new-onset organ failure (2% and 0%, respectively; p=1·00), bleeding (2% and 0%, respectively; p=1·00), perforation of a visceral organ or enterocutaneous fistula (2% and 2%, respectively; RR 0·87; 95% CI 0·06-13·51; p=1·00). The incidence of other outcomes, including incisional hernia (4% and 2%, respectively; RR 2·86; 95% CI 0·32-25·72; p=0·54), pancreaticocutaenous fistula (2% and 0%, respectively; p=1·00), and wound infection (2% and 5%, respectively; RR 0·44; 95% CI 0·04-4·64; p=0·60), did not differ significantly.

Recurrent acute pancreatitis and chronic pancreatitis occurred in 7 patients (15%) and 5 patients (11%) in the immediate-drainage group versus 5 patients (12%) and 2 patients (5%) in the postponed-drainage group (RR 1·53; 95% 0·48-4·85; p=0·47; RR 2·18; 95% 0·45-10·6; p=0·44), respectively.

One or more drainage procedures were required in 7 patients (15%) in the immediate-drainage group versus 3 patients (7%) in the postponed drainage group (RR 2·03; 95% CI 0·56-7·37; p=0·33) after the initial 6-month follow-up; of which one was initially treated with antibiotics alone. Signs of a disrupted or disconnected pancreatic duct were present in 3 of those patients (30%). No patient in both groups needed a necrosectomy after the initial 6-month follow-up. The median number of drainage procedures and necrosectomies was 0 [IQR 0] in both groups (p=0·28). More details regarding interventions are given in Supplementary Table S5, Supplemental Digital Content 1, http://links.lww.com/SLA/ E733. The median length of intensive care stay was 0 days [IQR 0] in both groups (p=0·69), and hospital stay was 0 days [IQR 16] in the immediate-drainage group and 2 [IQR 5] in the postponed-drainage group (p=0·09), respectively. Results of the sensitivity analyses are provided in Supplementary Table S6, Supplemental Digital Content 1, http://links.lww.com/SLA/ E733.

Table 1. Primary and secondary outcomes[a]

	New events after the initial 6-month follow-up (excluding events as initially reported in the POINTER trial)				**Total follow-up[b]** (time between randomization and the end of long-term follow-up)			
Outcome	**Immediate Drainage (*n* = 47)**	**Postponed Drainage (*n* = 41)**	**Relative risk (95% CI)**	**P-value**	**Immediate Drainage (*n* = 54)**	**Postponed Drainage (*n* = 46)**	**Relative risk (95% CI)**	**P-value**
Primary outcomes – no. (%)								
Major complications or death	7 (15)	7 (17)	0.87 (0.33-2.28)	0.78	26 (48)	21 (46)	1.06 (0.69-1.60)	0.80
Secondary outcomes – no. (%)[c]								
Death	4 (9)	4 (10)	0.87 (0.23-3.27)	1.00	11 (20)	9 (20)	1.04 (0.47-2.29)	0.92
New-onset organ failure	4 (9)	2 (5)	1.75 (0.34-9.04)	0.68	17 (31)	12 (26)	1.21 (0.65-2.26)	0.55
- Pulmonary	3 (6)	2 (5)	1.31 (0.23-7.45)	1.00	8 (15)	10 (22)	0.68 (0.29-1.58)	0.37
- Cardiovascular	3 (6)	1 (2)	2.62 (0.28-24.19)	0.62	13 (24)	10 (22)	1.11 (0.54-2.29)	0.78
- Renal	0	0	-	-	3 (6)	4 (9)	0.64 (0.15-2.71)	0.70
Multiple new-onset organ failure	1 (2)	0	-	1.00	5 (9)	8 (17)	0.53 (0.19-1.52)	0.23
Bleeding requiring intervention	1 (2)	0	-	1.00	8 (15)	10 (22)	0.68 (0.29-1.58)	0.37
Perforation of a visceral organ or enterocutaneous fistula	1 (2)	1 (2)	0.87 (0.06-13.51)	1.00	5 (9)	5 (11)	0.85 (0.26-2.76)	1.00
Other outcomes – no. (%)								
Incisional hernia	2 (4)	1 (2)	2.86 (0.32-25.72)	0.54	2 (4)	1 (2)	1.70 (0.16-18.2)	1.00
Pancreaticocutaneous fistula	1 (2)	0	-	1.00	7 (13)	4 (9)	1.49 (0.47-4.77)	0.50
Wound infection	1 (2)	2 (5)	0.44 (0.04-4.64)	0.60	1 (2)	3 (7)	0.28 (0.03-2.64)	0.33
Recurrent acute pancreatitis	7 (15)	5 (10)	1.53 (0.48-4.85)	0.47	n.a.	n.a.	n.a.	n.a.
Chronic pancreatitis	5 (12)	2 (5)	2.18 (0.45-10.6)	0.44	n.a.	n.a.	n.a.	n.a.

Data are presented as no. (%). [a]Multiple events in the same patient were scored as one outcome. [b]4 patients (of the originally 104 included patients) from the POINTER trial did not consent to participate in this follow-up study and were therefore missing in the total follow-up analysis. [c]Individual components of the composite primary outcome.

Total follow-up

In the total follow-up, the composite primary outcome of death and major complications occurred in 26/54 patients (48%) in the immediate-drainage group and in 21/46 patients (46%) in the postponed-drainage group (RR 1·06; 95% CI 0·69-1·60; p=0·80) (Table 1). Death occurred in 11 patients (20%) and 9 patients (20%) in the immediate-drainage group and postponed-drainage group, respectively. No differences were found in the individual components of major complications.

All 54 patients (100%) in the immediate-drainage group underwent catheter drainage in the total follow-up, whereas 30 patients (65%) in the postponed-drainage group (RR 1·53; 95% CI 1·24-1·89; p<0·0001) (Table 2). Necrosectomy was performed in 28 patients (52%) in the immediate-drainage group versus 11 patients (24%) in the postponed-drainage group (RR 2.17; 95% CI 1.22-3.86; p=0·001). Patients in the postponed-drainage group required fewer catheter drainages (1 [IQR 3] versus 3 [IQR 4]; p=0·00) and necrosectomies (1 [IQR 1] versus 2 [IQR 1]; p=0·01) compared with patients in the immediate-drainage group. The median number of surgical, endoscopic and radiologic interventions (catheter drainage and necrosectomy) was 4 [IRQ 5] in the immediate-drainage group versus 1 [IQR 6] in the postponed-drainage group (p=0.001).

Patients successfully treated with antibiotics only

Of the 17 patients in the postponed drainage group who survived the initial 6-month follow-up and were successfully treated with antibiotics only, for example, without any interventions, 2 patients did not provide informed consent to this study, leaving 15 patients to be included in these analyses. Of these patients, 14 patients (93%) remained without intervention at the end of long-term follow-up. Ultimately, 14 out of 44 patients (35%) assigned to the postponed-drainage group were successfully treated with antibiotics only in the total follow-up.

End of long-term follow-up

At the end of long-term follow-up, there were no differences in the new development of exocrine and endocrine pancreatic insufficiency (Table 3). The exocrine and endocrine pancreatic function over time is presented in Supplementary Table S7, Supplemental Digital Content 1, http://links.lww.com/SLA/ E733. The quality of life scores, SF-36 physical and mental health scores, at the end of long-term follow-up were also comparable among groups; the physical component scale was 49 (±14) and 43 (±22) (p=0·17) whereas the mental component scale was 43 (±8) and 42 (±9) (p=0·43) in the immediate- and postponed-drainage group, respectively.

Table 2. Interventions and health care utilization[a]

	New events after the initial 6-month follow-up (excluding events as initially reported in the POINTER trial)				**Total follow-up**[b] (time between randomization and the end of long-term follow-up)			
Outcome	**Immediate Drainage (*n* = 47)**	**Postponed Drainage (*n* = 41)**	**Relative risk (95% CI)**	**P-value**	**Immediate Drainage (*n* = 54)**	**Postponed Drainage (*n* = 46)**	**Relative risk (95% CI)**	**P-value**
Catheter Drainage – no. (%)	7 (15)	3 (7)	2.03 (0.56-7.37)	0.33	54 (100)	30 (65)	1.53 (1.24-1.89)	0.000
Necrosectomy – no. (%)	0	0	-	-	28 (52)	11 (24)	2.17 (1.22-3.86)	0.004
Median total surgical, endoscopic, and radiologic interventions for infected necrosis (IQR) – no.	0 (0-0)	0 (0-0)	-	0.28	4 (2-7)	1 (0-6)	-	0.001
Median total drainage procedures (IQR) - no.	0 (0-0)	0 (0-0)	-	0.28	3 (1-5)	1 (0-3)	-	0.000
No. of drainage procedures (%) – no. of patients (%)								
0	40 (85)	38 (93)	-	-	0	16 (35)	-	-
1	6 (13)	2 (5)	-	-	19 (35)	16 (35)	-	-
2	0	0	-	-	6 (11)	0	-	-
≥3	1 (2)	1 (2)	-	-	29 (54)	14 (30)	-	-
Median total necrosectomies (IQR) – no.	0 (0-0)	0 (0-0)	-	-	1 (0-1)	0 (0-0)	-	0.01
No. of necrosectomies – no. of patients (%)								
0	47 (100)	41 (100)	-	-	27 (50)	38 (82)	-	-
1	0	0	-	-	13 (24)	4 (9)	-	-
2	0	0	-	-	3 (6)	1 (3)	-	-
≥3	0	0	-	-	12 (22)	6 (13)	-	-
Median length of stay in ICU (IQR) – days	0 (0-0)	0 (0-0)	-	0.69	0 (0-16)	0 (0-10)	-	0.80
Median length of stay in hospital (IQR) – days related to pancreatitis	0 (0-16)	2 (0-5)	-	0.56	57 (37-90)	41 (22-76)	-	0.09

Data are presented as no. (%) or median (IQR). [a]Multiple events in the same patient were scored as one outcome. [b]4 patients (of the originally 104 included patients) from the POINTER trial did not consent to participate in this follow-up study and were therefore missing in the total follow-up analysis. ICU = intensive care unit.

Table 3. Pancreatic function and quality of life at the end of long-term follow-up[a]

Outcome	Immediate Drainage (*n* = 42)	Postponed Drainage (*n* = 37)	Relative risk (95% CI)	P-value
Exocrine pancreatic insufficiency				
Enzyme supplement use	18 (43)	13 (35)	1.22 (0.70-2.13)	0.48
Endocrine pancreatic insufficiency	18 (43)	13 (35)	1.22 (0.70-2.13)	0.48
Oral antidiabetics use only	5 (12)	2 (5)	2.20 (0.45-10.68)	0.44
Insulin use only	8 (19)	10 (27)	0.71 (0.31-1.60)	0.40
Oral antidiabetics and insulin use	5 (12)	1 (3)	4.41 (0.54-36.01)	0.21
Quality of Life (SF-36)				
PCS	49 (14)	43 (22)	-	0.17
MCS	43 (8)	42 (9)	-	0.43

Data are presented as no. (%) or mean (SD). [a]At the end of long-term follow-up, data from questionnaires were obtained from all but one surviving patients (n=79). PCS = Physical Component Scale. MCS = Mental Component Scale. The scores of both PCS and MCS range from 0 to 100, with higher scores indicating better quality of life.

DISCUSSION

This long-term follow-up study of the POINTER trial confirms that a postponed-drainage approach for infected necrotizing pancreatitis resulted in fewer interventions, as compared with immediate drainage, and almost a third of these patients were successfully treated with antibiotics only. Postponing or even omitting drainage does not lead to long-term adverse outcomes in patients with infected necrotizing pancreatitis.

In line with previous studies, no benefits of immediate drainage in comparison with delaying intervention were seen (12, 22-25). Nevertheless, one may argue that a subset of patients still benefit from an immediate approach, as in general the duration of organ failure impacts clinical outcomes (26). A recent pilot randomized controlled trial evaluated the optimal timing of percutaneous drainage in necrotizing pancreatitis with persistent organ failure as the primary indication and reported a beneficial trend for early drainage (27). But, the long-term outcomes of both approaches are only evaluated by 1 small non-randomized study, wherein no difference in regression and recurrence of collections were observed (25).

The most remarkable benefit of a postponed-drainage approach found in the initial POINTER trial was that 39% of patients assigned to the postponed-drainage group were treated with antibiotics alone (i.e. no catheter drainage or other intervention), with 35% of patients surviving the trials' initial 6-month follow-up (11). In the

current long-term follow-up study, this benefit continued in 93% of the surviving patients as the intervention was required in 1 initially conservatively treated patient. It is noteworthy that this patient declined cholecystectomy following the initial episode of acute biliary pancreatitis and subsequently developed recurrent acute pancreatitis with infected pancreatic necrosis.

In the total follow-up period, 35% of patients were successfully treated with antibiotics only. It should be pointed out here that the majority of patients did not suffer from (multiple) organ failure at randomization (Supplementary Table S2, Supplemental Digital Content 1, http://links.lww.com/SLA/ E733). This is in line with previous studies that have reported similar success rates of antibiotic treatment (range 3% to 39%) in selected patients with infected necrotizing pancreatitis, mostly in patients without organ failure. Future studies will have to confirm the optimal selection criteria for antibiotic treatment, in which procalcitonin should be considered (28), and determine details of treatment, including aspects of antibiotic stewardship. A prediction model selecting patients for an antibiotics-only-approach would be useful and should be developed.

As the results of this study will further enhance the use of antibiotic treatment, efforts to optimize the quality of its use should be made (29). A recent Dutch study evaluated antibiotic use and obtained pancreatic cultures of patients with infected necrotizing pancreatitis, and found that 48% received inappropriate empirical broad-spectrum antibiotics based on the identified microorganisms (30). Another concern about antibiotic (over)use, which in turn has a great impact on antibiotic resistance, is that antibiotics are often not tailored to (FNA-)culture results. Furthermore, the optimal treatment duration for infected necrosis is unknown. We hypothesize that an antibiotic stewardship-driven approach, which includes recommendations on FNA, and the timing and duration of antibiotic treatment, will result in similar patient outcomes and health care use, as compared with current practice.

During the present long-term follow-up, after the initial 6-month period, necrosectomy was not performed in any patient, meaning that 51% of patients in the immediate-drainage group and 22% of patients in the postponed-drainage group underwent necrosectomy ($p=0.004$) in the total follow-up. This is lower than the 51% to 60% rates of necrosectomy previously reported in patients with infected necrotizing pancreatitis treated with the step-up approach (17, 31). However, also both these studies stated a negligibly low need for additional necrosectomy after the 6-month follow-up. Another long-term benefit of postponed drainage includes the decreased need for drainage procedures and necrosectomy. The question remains whether postponing drainage through encapsulation of the necrotic collection, actually enables

a more effective drainage procedure, thereby making multiple procedures and even necrosectomy redundant (32).

At the end of long-term follow-up, pancreatic function (i.e. exocrine and endocrine) did not differ between the 2 groups. Both exocrine and endocrine insufficiency were present in 43% of patients in the immediate-drainage group and 35% in the postponed-drainage group. Previous literature that evaluated late-onset exocrine insufficiency showed similar prevalence rates (17, 31, 33), underlining the importance of monitoring exocrine pancreatic function over time. In our study, the fecal elastase-1 test was only performed in 61% of patients during long-term follow-up. Moreover, we showed that 22% of patients developed endocrine pancreatic insufficiency after the initial 6-month follow-up. It remains unclear, however, how this should be interpreted, since we cannot clearly differentiate between post-pancreatitis diabetes and the occurrence of new-onset type 2 diabetes (34). Quality of life was similar in both groups. Other long-term follow-up studies in necrotizing pancreatitis patients showed similar quality of life scores, wherein the hypothesis is that over the years, patients adapt to their morbidity and thereby the quality of life improves when compared with the baseline (17, 35, 36)

There are several limitations that need to be taken into account when interpreting the results of this study. First, the sample size was relatively small, although this study represents the largest follow-up study evaluating both approaches. Second, the long-term follow-up period was not standardized. As a result, the duration of follow-up differed between the first and last randomized patient, ranging from 7 years to 2.5 years, respectively. However, in the postponed-drainage group, all first drainage procedures after the initial 6-month follow-up were performed in the first 2 years after randomization with the exception of one (Supplementary Table S5, Supplemental Digital Content 1, http://links.lww.com/SLA/ E733). In addition, the total follow-up time did not differ between treatment groups. Third, the decision to intervene after the initial 6-month follow-up was not standardized. Nonetheless, the DPSG utilizes a nationwide expert panel (37), which helps minimize treatment variation and inequivalent access to specialized care. In cases where the patient showed no improvements with antibiotics, our experts recommended catheter drainage. If drainage had already been performed, further steps such as a new computed tomography scan and potential drain revision/upgrade, or necrosectomy, were advised. Fourth, some data (e.g. complications, intervention, hospital stay) were collected retrospectively which may have led to information bias. Fifth, endocrine and exocrine pancreatic function were pragmatically evaluated based on the use of medication and therefore, do not always reflect the accurate status of pancreatic insufficiency. The main strength is the

long-term follow-up of the multicenter randomized POINTER trial in a cohort of patients with infected necrotizing pancreatitis.

CONCLUSION

Postponed catheter drainage, using antibiotics, may be seen as the preferred approach when treating patients with infected necrotizing pancreatitis. Delaying drainage reduces the number of interventions and offers the opportunity to effectively treat patients with antibiotic treatment only without increased risk for adverse long-term outcomes. The decision to postpone intervention, however, should be individualized and based on the patient's clinical course and improvement on antibiotics. Further research in this field, including the exact role of antibiotics in the management of infected necrosis, is encouraged.

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Supplementary table S1. STROBE checklist

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 3
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 4
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 6-7
Bias	9	Describe any efforts to address potential sources of bias	N.A.
Study size	10	Explain how the study size was arrived at	N.A.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 7-8
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	Page 9 / Figure 1
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	

Supplementary table S1. STROBE checklist (*continued*)

	Item No	Recommendation	Page No
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Supplementary Table S3
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 9-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 9-11
		(*b*) Report category boundaries when continuous variables were categorized	N.A.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N.A.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 13-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 8

**Give information separately for exposed and unexposed groups. Information on the STROBE Initiative is available at http://www.strobe-statement.org.*

Supplementary table S2. Definitions of the primary and secondary outcomes

Outcome	Definition
Primary outcome	The primary outcome was a composite of death and major complications.
Secondary outcomes	
• Major complications	
New onset organ failure	Organ failure occurring after randomization and not present 24 hours before randomization: - Pulmonary: a PaO2 < 60 mmHg despite FiO2 30% or the need for mechanical ventilation - Cardiovascular: a systolic blood pressure < 90 mmHg despite adequate fluid resuscitation or need for vasopressor support - Renal: a serum creatinine > 177 mmol/L after rehydration or need for hemofiltration or hemodialysis (in case patients already suffered from renal insufficiency before this episode of AP [creatinine > 177 umol/L] this does not count as renal failure)
Multiple organ failure	Failure of 2 or more organ systems (i.e. respiratory, cardiovascular or renal) at the same moment.
Bleeding requiring intervention	Bleeding requiring surgical, radiologic, or endoscopic intervention.
Perforation of a visceral organ requiring intervention	Perforation requiring surgical, radiologic, or endoscopic intervention.
Enterocutaneous fistula requiring intervention	Secretion of fecal material from a percutaneous drain or drainage canal after removal of drains or from a surgical wound, either from small or large bowel; confirmed by imaging or during surgery.
• Other outcomes	
Incisional hernia	Incisional hernia is defined as full-thickness discontinuity in abdominal wall and bulging of abdominal contents, with or without obstruction.
Pancreaticocutaneous fistula	Output through a percutaneous drain or drainage canal after removal of drains from a surgical wound, or any measurable volume of fluid with an amylase content >3 times the serum amylase level.

Supplementary table S2. Definitions of the primary and secondary outcomes (*continued*)

Wound infection	A superficial incisional SSI (surgical site infection) and must meet the following criterion: infection occurs within 30 days after the operative procedure and involves only skin and subcutaneous tissue of the incision and the patient has at least 1 of the following: - Purulent drainage from the superficial/deep incision but not from the organ/space component of the surgical site - Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision - At least 1 of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, and superficial incision is deliberately opened by surgeon and is culture positive or not cultured. A culture-negative finding does not meet this criterion - An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathological or radiologic examination - Diagnosis of superficial/deep incisional SSI by the surgeon or attending physician
Exocrine pancreatic insufficiency	Oral pancreatic-enzyme supplementation required to treat clinical symptoms of steatorrhea; this requirement was not present before onset of pancreatitis.
Endocrine pancreatic insufficiency	The need for insulin or oral-diabetic drugs; this requirement was not present before onset of pancreatitis.
Recurrent acute pancreatitis	Recurrence of acute pancreatitis is defined as a new episode of acute pancreatitis, as defined by the 2012 Revised Atlanta criteria, after complete resolution of all symptoms associated with the previous acute pancreatitis episode.
Chronic pancreatitis	Defined according to the M-ANNHEIM criteria.

Supplementary table S3. Baseline characteristics of the POINTER trial

Characteristics	**Immediate Drainage (*n* = 55)**	**Postponed Drainage (*n* = 49)**
Age (yr)	60 (14)	59 (11)
Male sex	32 (58)	32 (65)
Cause of pancreatitis		
Gallstones	36 (65)	29 (59)
Alcohol abuse	8 (15)	7 (14)
Disease severity		
Admitted to intensive care unit	15 (27)	13 (27)
SIRS	47 (85)	40 (82)
Organ failure	13 (24)	8 (16)
Multiple organ failure	8 (15)	6 (12)
CT severity index[a]	7 ± 2	6 ± 2
Extent of pancreatic necrosis		
<30%	35 (64)	33 (68)
30-50%	8 (15)	7 (14)
>50%	12 (22)	9 (18)
Encapsulation of necrosis		
Not encapsulated	6 (11)	8 (16)
Medium encapsulated	16 (29)	19 (39)
Largely encapsulated	19 (35)	11 (22)
Fully encapsulated	14 (25)	11 (22)
Diagnosis of infected necrosis		
Gas configuration	20 (36)	16 (33)
Positive fine needle aspiration	6 (11)	11 (22)
Suspected clinically	29 (53)	22 (45)
Onset of symptoms to diagnosis of necrotising pancreatitis/ necrotic collection (days)	8 ± 8	9 ± 7
Onset of symptoms to diagnosis of infected necrosis (days)	21 ± 6	19 ± 7

Data are presented as no. (%) or mean (SD). CT = computed tomography, SIRS = Systemic Inflammatory Response Syndrome. [a]Data were derived from the contrast-enhanced CT performed before randomization. Scores may range from 0 to 10, with higher scores indicating more extensive pancreatic and peripancreatic necrosis.

Supplementary table S4. All-cause mortality after the initial 6-month follow-up per individual patient

Immediate-drainage	**Cause of death**	**Age**	**Pancreatitis related**	**Time (months)[a]**
1	Obstructive shock of unknown cause	72	No	8
2	Multiple causes not related to pancreatitis	69	No	9
3	Fistula of the gastrointestinal-tract (patient requested life-sustaining treatment withdrawal)	70	Yes	10
4	Infected pancreatic necrosis in combination with COVID-19 infection (patient requested life-sustaining treatment withdrawal)	57	Yes	48
Postponed-drainage	**Cause of death**	**Age**	**Pancreatitis related**	**Time (months)[a]**
1	Cholangiocarcinoma	57	No	26
2	Gastric cancer	75	No	44
3	Respiratory failure of unknown cause	56	No	57
4	Lung cancer	74	No	62

[a] *Time between randomization and date of death.*

Supplementary table S5. Drainage procedures after the initial 6-month follow-up per individual patient

Immediate-drainage	**Type of drainage**	**Indication**	**Time (months)** [a]
1	- PCD (5x)	Persistent pancreatic fluid collection	7
2	- PCD	Recurrent pancreatic fluid collection (recurrent acute pancreatitis)	49
3	- PCD	Persistent pancreatic fluid collection (disconnected pancreatic duct)	20
4	- ETD	Recurrent pancreatic fluid collection	7
5	- ETD	Recurrent pancreatic fluid collection (disconnected pancreatic duct)	9
6	- PCD	Recurrent pancreatic fluid collection (disconnected pancreatic duct)	23
7	- ETD	Persistent pancreatic fluid collection	15
Postponed-drainage	**Type of drainage**	**Indication**	**Time (months)** [a]
1	- PCD	Persistent pancreatic fluid collection	11
2	- ETD	Recurrent pancreatic fluid collection (recurrent acute pancreatitis)	22
3	- ETD - PCD (20x)	Recurrent infected necrotic collections (recurrent acute pancreatitis)	19

Patients per group who required (additional) drainage procedures after the initial 6-months follow-up. ETD = endoscopic transluminal drainage. PCD = percutaneous catheter drainage. [a] Time between randomisation and date of first drainage procedure after the initial 6-months follow-up.

Supplementary table S6. Sensitivity analyses: Primary outcome and interventions in patients whom diagnosis was based on clinical suspicion for infected necrosis[a]

	New events after the initial 6-month follow-up (excluding events as initially reported in the POINTER trial)				**Total follow-up**[b] (time between randomization and the end of long-term follow-up)			
Outcome	**Immediate Drainage (*n* = 24/47)**	**Postponed Drainage (*n* = 18/41)**	**Relative risk (95% CI)**	**P-value**	**Immediate Drainage (*n* = 29/54)**	**Postponed Drainage (*n* = 20/46)**	**Relative risk (95% CI)**	**P-value**
Primary outcome								
Major complications or death – no. (%)	3 (13)	3 (17)	0.75 (0.17-3.29)	1.00	15 (52)	9 (45)	1.15 (0.63-2.09)	0.64
Interventions								
Catheter Drainage – no. (%)	4 (17)	3 (17)	1.00 (0.26-3.92)	1.00	29 (100)	14 (70)	1.43 (1.07-1.90)	0.00
Necrosectomy – no. (%)	0	0	-	-	18 (62)	4 (20)	3.10 (1.24-7.80)	0.00
Median total surgical, endoscopic, and radiologic interventions for infected necrosis (IQR) – no.	0 (0-0)	0 (0-0)	-	0.94	4 (2-7)	2 (0-5)	-	0.06
Median total drainage procedures (IQR) - no.	0 (0-0)	0 (0-0)	-	0.94	2 (1-5)	1 (0-4)	-	0.07
No. of drainage procedures (%) – no. of patients (%)								
0	20 (83)	15 (83)	-	-	0	6 (30)	-	-
1	4 (17)	2 (11)	-	-	13 (45)	7 (35)	-	-
2	0	0	-	-	2 (7)	0	-	-
≥3	0	1 (1)	-	-	14 (48)	7 (35)	-	-
Median total necrosectomies (IQR) – no.	0 (0-0)	0 (0-0)	-	-	1 (0-3)	0 (0-0)	-	0.03
No. of necrosectomies – no. of patients (%)								
0	24 (100)	18 (100)	-	-	11 (38)	16 (80)	-	-
1	0	0	-	-	6 (21)	0	-	-
2	0	0	-	-	3 (10)	0	-	-
≥3	0	0	-	-	9 (31)	4 (20)	-	-

Data are presented as no. (%) or median (IQR). [a]Multiple events in the same patient were scored as one outcome. [b]4 patients (of the originally 104 included patients) from the POINTER trial did not consent to participate in this follow-up study and were therefore missing in the total follow-up analysis. ICU = intensive care unit.

Supplementary table S7. Exocrine and endocrine pancreatic function over time[a]

Outcome	Total (n=79)	Immediate Drainage (*n* = 42)	Postponed Drainage (*n* = 37)
Exocrine pancreatic insufficiency[b]			
No	42 (53)	23 (55)	19 (51)
Recovered	6 (8)	1 (2)	5 (14)
Persistent	25 (32)	15 (36)	10 (27)
New-onset	6 (8)	3 (7)	3 (8)
Endocrine pancreatic insufficiency[c]			
No	44 (56)	23 (55)	21 (57)
Recovered	4 (5)	1 (2)	3 (8)
Persistent	14 (18)	7 (18)	7 (19)
New-onset	17 (22)	11 (26)	6 (16)

Data are presented as no. (%). [a]Pancreatic function at the end of long-term follow-up compared to the pancreatic function at 6-month follow-up. Data from questionnaires were obtained from all but one surviving patients (n=79).[b] Defined as pancreatic enzyme use. [c]Defined as diabetes medication use.

PART II

Splanchnic vein thrombosis in acute pancreatitis

CHAPTER 3

Therapeutic anticoagulation for splanchnic vein thrombosis in acute pancreatitis: *a systematic review and meta-analysis*

Pancreatology 2022

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ABSTRACT

Objectives: The optimal management of patients with acute pancreatitis (AP) and splanchnic vein thrombosis (SVT) remains unknown. This systematic review and meta-analysis aimed to see if therapeutic anticoagulation (AC) improves outcomes in patients with AP and SVT.

Methods: A systematic review was performed according to PRISMA guidelines. Main outcomes were recanalization, recurrent venous thromboembolism, development of varices, collaterals or cavernoma, haemorrhage and mortality. Meta-analysis were performed with the Mantel-Haenszel random effect models.

Results: Seven retrospective cohort studies (3495 patients) were included. SVT occurred in 233 (7%) patients and involved most frequently the splenic vein (44%). Therapeutic AC was administered to 109 (47%) patients, most frequently to those with triple vessel thrombosis (72%) and least to those with isolated splenic vein (22%) or superior mesenteric vein thrombosis (0%). Most studies administered (low molecular weight) heparin followed by warfarin (duration ranged between 1.5 and 12 months). This meta-analysis showed an absolute risk difference of 9% (95% confidence interval [CI] = -11-28%) for recanalization, -3% (95% CI = -19-12%) for the development of varices, collaterals or cavernoma, 3% (95% CI = -6-12%) for hemorrhage and 2% (95% CI = -8-12%) for mortality.

Conclusions: Based on the currently available data, it remains unclear if therapeutic anticoagulation provides benefit to acute pancreatitis patients with splanchnic vein thrombosis. These results are based on low quality data underlining the need for further higher quality studies.

INTRODUCTION

Acute pancreatitis (AP) may be complicated by splanchnic vein thrombosis (SVT) affecting the splenic vein (SpIV), portal vein (PV) and superior mesenteric vein (SMV), either isolated or effecting several venous segments (1, 2). This typically occurs in patients that develop moderate or severe AP with (peri)pancreatic necrosis or fluid collections (3). Although the pathophysiology underlying SVT in AP is incompletely understood, it is believed that the inflammatory state, along with the direct mass of fluid collections, facilitate venous stasis and activation of coagulation, leading to thrombosis (4, 5). Persisting vascular obstruction in the splanchnic circulation may lead to several complications such as portal hypertension, small bowel ischemia or hepatic failure (6).

Treatment of SVT with therapeutic anticoagulation (AC) aims at preventing progression of thrombosis and recurrent venous thromboembolism (VTE) (7). On the other hand, therapeutic levels of AC are associated with a considerable risk of haemorrhage, e.g. related to portal hypertension and pseudoaneurysms (8, 9). The current guidelines consider that the benefits of therapeutic AC outweigh the risks in patients with acute symptomatic SVT in the absence of contraindications (8-11). However, several barriers exist for clinicians to apply these guidelines to patients with AP and SVT. First, AP-induced SVT is usually asymptomatic and detected incidentally through imaging (12, 13). Second, the available studies on which the guidelines are based have mainly focused on patients with persistent thrombotic risk (14, 15), who may, from a pathophysiological point of view, benefit from a different treatment strategy. Finally, patients with AP pose other challenges because of the risk of haemorrhage associated with the frequent need for invasive interventions (such as drainage and necrosectomy) (7). Therefore, in daily practice, the risk of haemorrhage may increase the threshold for clinicians to use therapeutic AC in patients with AP-induced SVT.

Previously, one meta-analysis and one systematic review have evaluated the benefits and risks of therapeutic AC in patients with AP and SVT (16, 17). The meta-analysis suggested that routine use of therapeutic AC does not provide any benefit to the patient and the systematic review concluded that evidence was too limited to draw any conclusion. However, both studies were limited by data unavailability. For this reason, an updated comprehensive systematic review and meta-analysis may shed new light on the unanswered question whether therapeutic AC is indicated for SVT in the context of AP.

The aim of this systematic review and meta-analysis was to determine if therapeutic AC improves clinical outcomes in patients with AP and SVT.

METHODS

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (18) and was registered with PROSPERO (CRD42021224941).

Literature search

Guided by a librarian, PubMed, Embase, Web of Science and Cochrane library databases were searched for relevant literature published until December7th 2020. Search terms included 'pancreatitis', 'thrombosis', 'vascular complications' and multiple synonyms. The complete literature search is provided in Appendix S1 (supporting information). All reference lists of included studies were screened to identify any additional relevant studies.

Study selection

Two independent reviewers (J.V.G. & D.K.) screened the titles, abstracts, full texts of all obtained articles for the potential to meet the eligibility criteria and discrepancies were resolved by consensus. Studies were included if the following predefined inclusion criteria were met: randomized controlled trial or observational cohort study written in English, published until December 7th 2020, including AP patients with SVT and reporting at least one outcome of interest (i.e. it was not mandatory that all outcomes of interest were reported in the study). Literature reviews, case reports and case series were excluded.

Data collection

A predefined standardized data extraction form was used by two independent reviewers (J.V.G. & D.K.) to extract study information: author, year, journal, nation, study design time period, inclusion criteria, no. of patients, definitions of AP, no. of SVT, localization of thrombosis, definition of thrombosis, no. of patients treated with therapeutic AC, no. of patients not treated with therapeutic AC, radiological follow-up, recanalization, recurrent VTE, varices/collaterals/cavernoma, haemorrhage and mortality and discrepancies were resolved by consensus.

Outcomes and comparison

The main outcomes were recanalization, recurrent VTE, development of varices/collaterals/cavernoma, haemorrhage and mortality. Diagnosis of SVT was based on imaging techniques (i.e. CT, MRI or colour Doppler ultrasonography) and included direct and indirect findings of SVT (e.g. thrombus detection, luminal narrowing or presence of collaterals). Recanalization was defined as reported by the studies (e.g. complete recanalization of SVT evaluated through imaging at the end of the intervention or

six months after diagnosis). Recurrent VTE was defined as deep vein thrombosis, pulmonary embolism or recurrent SVT. Varices/collaterals/cavernoma were pooled together as definitions partly overlap and all describe an altered venous anatomy (e.g. presence of large portoportal collaterals and/or abundance of collateral veins). Haemorrhage was defined as reported by the studies (e.g. both major and minor haemorrhage). Mortality was defined as reported by the studies (e.g. in-hospital mortality or mortality within a month of discharge). Patients who received therapeutic AC were compared with patients who did not receive therapeutic AC. Of note, most of these latter patients received anticoagulation at a prophylactic dose. Attempts were made to perform subgroup analysis to estimate the effects of various SVT characteristics (i.e. risk factors and localization, extent and age of thrombosis) and treatment variables (i.e. type and duration of therapeutic AC therapy).

Risk of bias

Two independent reviewers (J.V.G. & D.K.) determined the risk of bias according to the ROBINS-I (19) and discrepancies were resolved by consensus. Possible publication bias was assessed visually through funnel plots.

Statistical analysis

All analyses were performed using Review Manager (RevMan version 5·3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). For description of the study cohorts, categorical variables are presented as numbers (percentages). The I^2 statistic was used to assess between study heterogeneity. An I^2 value greater than 50% was considered as evidence for substantial heterogeneity. Mantel-Haenszel random effects models were used to calculate pooled effects are presented as absolute risk differences with 95% confidence interval (CI). Sensitivity analysis were performed with a Mantel-Haenszel fixed effects models. Two-tailed $P<0.05$ was considered as statistical significance.

Confidence in evidence

The strength of the evidence and recommendations provided by this systematic review was assessed by the Grading of Recommendations Assessment, Development and Evaluation system (20).

RESULTS

Study selection and characteristics

The literature search identified 525 unique studies (Figure 1). Of these studies, seven retrospective studies (2, 21-26) were included in qualitative and quantitative synthesis (Table 1).

Table 1. Study characteristics

Author	Year	Nation	Design	Time period	Inclusion criteria	Definition of AP	No. of patients	Definition of SVT	No. (%) of SVT	Localization of SVT	No. (%) tAC	tAC	Standardized radiological follow-up
Gonzelez	2011	UK	Retro	2008-2009	AP	Atlanta classification	127	Imaging of venous complications	20 (19%)	SplV 40% PV 25% SMV 5% SpIV+PV 20% SpIV+SMV 5% SpIV+PV+SMV 5%	4 (20%)	LMWH, subsequently warfarin	No
Harris	2013	USA	Retro	1996-2006	AP	Atlanta classification	2454	Thrombus detection/ compressed vein/collaterals	45 (2%)	SpIV 38% PV 16% SMV 9% SpIV+PV 9% SpIV+SMV 9% PV+SMV 9% SpIV+PV+SMV 11%	17 (38%)	LMWH or unfractionated heparin, subsequently warfarin	Yes
Easler	2014	USA	Retro	2003-2010	AP	-	122	Luminal filling defect	22 (18%)	SpIV 59% PV 5% SMV 5% SpIV+PV 9% PV+SMV 5% SpIV+PV+SMV 18%	6 (27%)	Anticoagulation	No

Toqué	2015	France	Retro	2007-2012	AP	Rev. Atlanta classification	318	-	19 (6%)	SplV 37% PV 32% SplV+SMV 21% SplV+PV+SMV 11%	15 (79%)	Therapeutic anticoagulation	No
Garret	2018	France	Retro	2012-2015	(moderate) severe AP	Rev. Atlanta classification	148	CT findings	76 (52%)	SpIV 82%	39 (51%)	Anticoagulant therapy	No
Pagliari	2020	Italy	Retro	2015-2018	AP	Rev. Atlanta classification	221	Imaging of venous complications	27 (12%)	SplV 33% PV 4% SpIV+PV 7% SplV+SMV 37% PV+SMV 4% PV+SMV+SplV 15%	16 (59%)	LMWH, subsequently warfarin (7), fondaparinux (5), apixaban (4)	Yes
Junare	2020	India	Retro	2018	AP	Revised Atlanta classification	105	Thrombus detection/ compressed vein/collaterals	24 (23%)	SplV 46% SplV+PV 17% SplV+PV+SMV 38%	12 (50%)	Heparin, subsequently warfarin	No

Abbreviations: AP acute pancreatitis, PV portal vein, SpIV splenic vein, SMV superior mesenteric vein, SVT splanchnic vein thrombosis, tAC therapeutic anticoagulation.

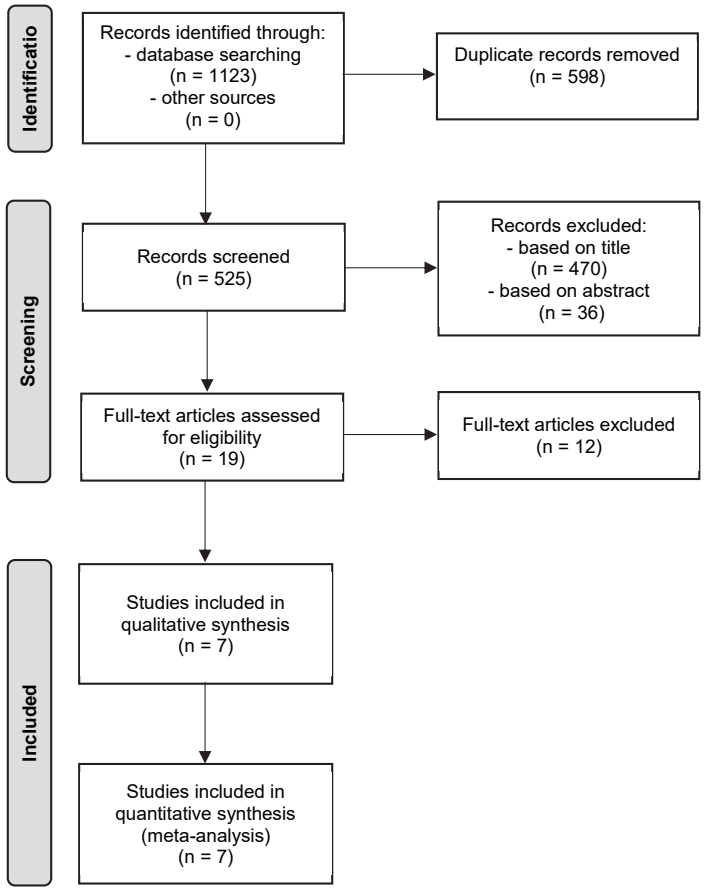

Figure 1. PRISMA flowchart

Four studies were conducted in Europe (2, 23-25), two studies were conducted in the United States of America (21, 22) and one study was conducted in India (26). The inclusion period of the studies ranged between 1996 and 2018.

In total, 3495 patients with AP were included. Among these patients, 233 (7%) developed SVT (range between studies 2-52%). The most common localization of SVT was the SplV (33-82%), followed by the PV (4-32%) and the SMV (5-9%). Combinations of involved veins were also reported in six studies (2, 21-23, 25, 26). The combinations of involved splanchnic veins were SplV+PV+SMV (5-38%), SplV+SMV (5-37%), SplV+PV (7-20%) and PV+SMV (4-9%). Of those diagnosed with SVT, at least 208 (89%) suffer from moderate severe or severe AP according to the revised Atlanta classification (27). Five studies (2, 21, 22, 25, 26) reported 93 of 138 patients (67%) with necrotizing AP and one study (24) reported explicitly on the presence of infected pancreatic necrosis in 47 of 67 patients (70%) (data not shown).

Of 233 AP patients with SVT, 109 (47%) were treated with therapeutic AC (range between studies 20-79%). Four studies reported on the localization of SVT and the treatment of choice in 93 patients (2, 22, 25, 26) (Table 2). Most notably, 13 out of 18 (72%) patients with SpIV+PV+SMV thrombosis received therapeutic AC, whereas none and only 9 out of 41 (22%) patients with SMV- and SpIV thrombosis were treated with therapeutic AC. At all other anatomic sites, patients with and without therapeutic AC were largely comparable. The patients in the therapeutic AC group were treated with Low Molecular Weight Heparin, followed by a vitamin K antagonist in three studies (2, 21, 25) with heparin, followed by a vitamin K antagonist in two studies (21, 26), with apixaban in one study (25), with fondaparinux in one study (25) and undefined in three studies (22-24). Standardized radiological follow-up was described in two studies (21, 25).

Table 2. Location of SVT in patients treated with therapeutic AC

		Anticoagulated	
Thrombosed vessel(s)	**No. (%)**	**No. (%)**	**Range between studies**
SpIV	41 (44%)	9 (22%)	0-56%
PV	7 (8%)	3 (43%)	0-100%
SMV	2 (2%)	0	-
SpIV+PV	12 (13%)	7 (58%)	50-100%
SpIV+SMV	11 (12%)	5 (46%)	0-50%
PV+SMV	2 (2%)	1 (50%)	0-100%
SpIV+PV+SMV	18 (19%)	13 (72%)	0-75%

Abbreviations: PV portal vein, SpIV splenic vein, SMV superior mesenteric vein, SVT splanchnic vein thrombosis, AC anticoagulation.

Risk of bias within studies

The overall risk of bias for all studies was judged as moderate (Table 3). This is mostly due to the moderate risk of confounding in all studies. The follow-up was not (adequately) stated in five studies (2, 22-24, 26) and the risk of bias in the measurement of outcomes was judged as moderate.

Main outcomes

Six studies (2, 21-23, 25, 26) reported on recanalization in 153 patients, which occurred in 25 of 70 patients (36%) with therapeutic AC (range between studies 0-69%) versus 17 of 83 patients (20%) without therapeutic AC (range between studies 11-42%). The absolute risk difference in recanalization between patients with therapeutic AC and without therapeutic AC was 9% (95% CI = -0.11-0.28. I^2=48%) (Figure 2A).

Table 3. Risk of bias according to the ROBINS-I tool

Author	Confounding	Selection of participants	Classification of intervention	Deviations of intended interventions	Missing data	Measurement of outcomes	Selection of reported results	Overall risk of bias
Gonzelez	Moderate	Low	Low	Low	Low	Moderate[2]	Low	**Moderate**
Harris	Moderate	Low	Low	Low	Low	Moderate[1]	Low	**Moderate**
Easler	Moderate	Low	Low	Low	Low	Moderate[2]	Low	**Moderate**
Toqué	Moderate	Low	Low	Low	Low	Moderate[2]	Low	**Moderate**
Garret	Moderate	Low	Low	Low	Low	Moderate[2]	Low	**Moderate**
Pagliari	Moderate	Low	Low	Low	Low	Low	Low	**Moderate**
Junare	Moderate	Low	Low	Low	Low	Moderate[2]	Low	**Moderate**

[1]*Only patients having unexplained pain underwent CT at diagnosis.* [2]*Follow up not stated or insufficient.*

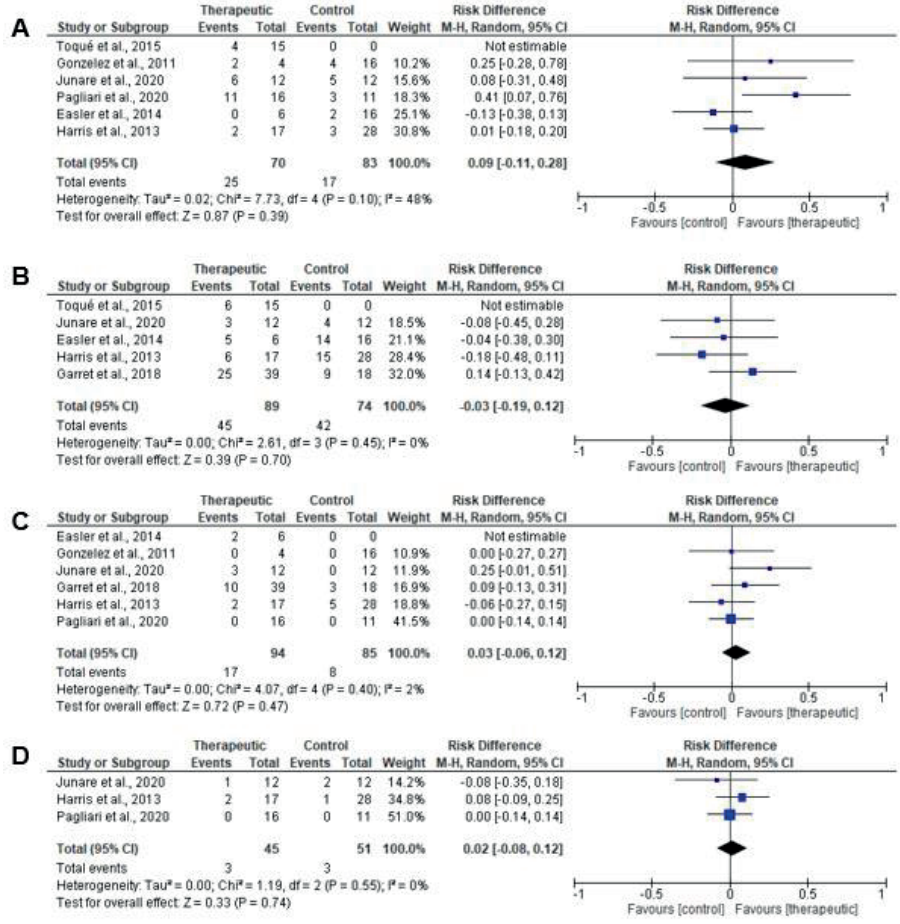

Figure 2. Meta-analysis for recanalization (A), varices, collaterals or cavernoma (B), hemorrhage (C), and mortality (D) with a random-effects model

Only one study (25) briefly mentioned on recurrent VTE in 27 patients and reported no SVT recurrence or VTE in other anatomic sites in patients treated with and without therapeutic AC.

Five studies (2, 21, 22, 24-26) reported on the development of varices/collaterals/cavernoma in 163 patients, which occurred in 45 of 89 patients (51%) with therapeutic AC (range between studies 25-83%) versus 42 of 74 patients (57%) without therapeutic AC (range between studies 33-88%). The absolute risk difference in varices/collaterals/cavernoma between patients with therapeutic AC and without therapeutic AC was -3% (95% CI = -0.19-0.12. I^2=0%) (Figure 2B).

Six studies (2, 21, 22, 24-26) reported on haemorrhage in 108 patients, which occurred in 17 of 94 patients (18%) with therapeutic AC (range between studies 0-33%) versus eight of 104 patients (8%) without therapeutic AC (range between studies 0-18%). The absolute risk difference in haemorrhage between patients with therapeutic AC and without therapeutic AC was 3% (95% CI = -0.06-0.12. I^2=2%) (Figure 2C).

Three studies (21, 25, 26) reported on mortality in 96 patients, which occurred in three of 45 patients (7%) with therapeutic AC (range between studies 0-12%) versus three of 51 patients (6%) without therapeutic AC (range between studies 0-17%). The absolute risk difference in mortality between patients with therapeutic AC and without therapeutic AC was 2% (95% CI = -0.08-0.12. I^2=0%) (Figure 2D).

Sensitivity analysis with a Mantel-Haenszel fixed effect models for all outcomes are provided in Figure S1 (supporting information) and showed similar results. With respect to the main outcomes, only two studies reported data on the localization of SVT (2, 25) one on the duration of treatment (25) and no studies reported data on the extent and age of thrombosis and the type of AC agent. Due to this limited information, subgroup analysis were not performed.

Risk of bias across studies

The funnel plots showed a fairly symmetrical scatter around the mean for all outcomes (Figure 3).

Confidence in evidence

The quality of evidence was judged as very low for all outcomes (table 4). Recanalization was downgraded due to serious risk of bias, indirectness and imprecision. The outcomes of recurrent VTE, haemorrhage and mortality was downgraded due to risk of bias. In addition, the outcome of varices/collaterals/varices was downgraded due to risk of bias and indirectness.

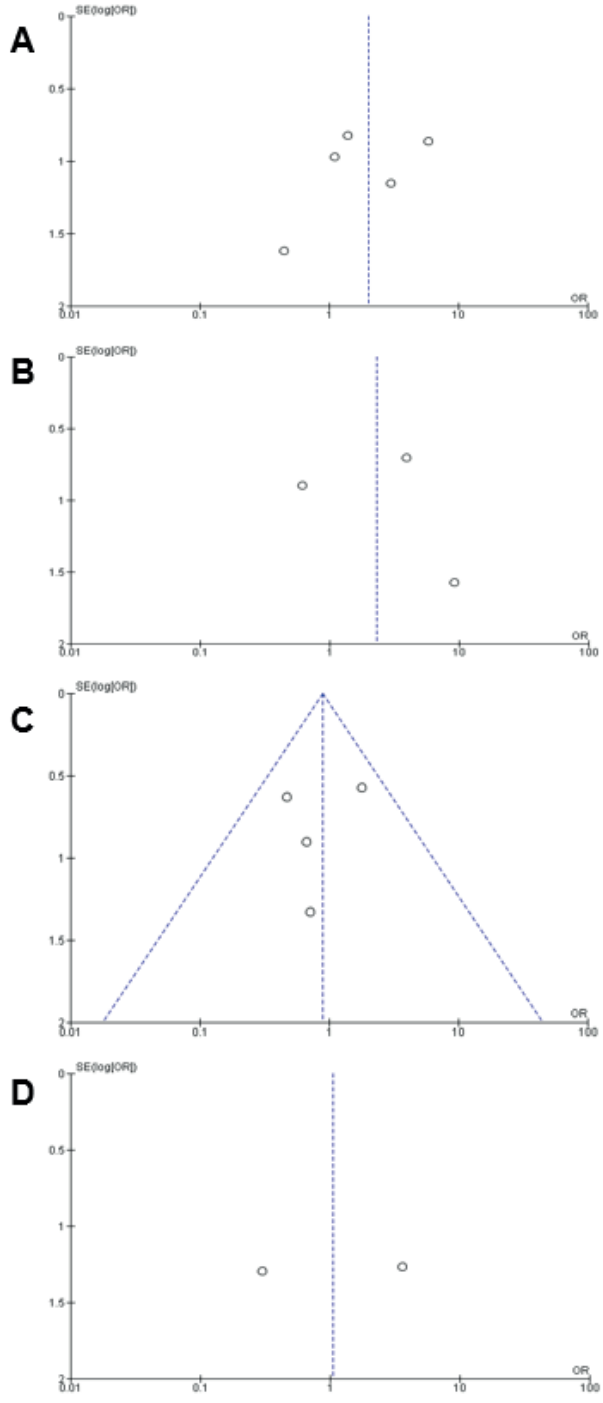

Figure 3. Funnel plots for recanalization (A), varices, collaterals or cavernoma (B), hemorrhage (C), and mortality (D)

Table 4. Quality assessment according to GRADE

		Quality assessment				
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality of evidence**
Outcome: recanalization						
6	Observational studies	Serious[2]	No serious	Serious[4]	Serious[5]	Very low
Outcome: recurrent venous thromboembolism						
1	Observational studies	Serious[2]	-	No serious	No serious	Very low
Outcome: varices/collaterals/cavernoma						
5	Observational studies	Serious[2]	No serious	Serious[4]	No serious	Very low
Outcome: hemorrhage						
6	Observational studies	Serious[1]	No serious	No serious	No serious	Very low
Outcome: mortality						
3	Observational studies	Serious[3]	No serious	No serious	No serious	Very low

[1]Downgraded one level for serious risk of bias due to confounding, it is possible that patients with a higher bleeding risk were less likely to have been given therapeutic anticoagulation. [2]Downgraded one level for serious risk of bias in the measurement of outcomes, it is uncertain if a standardized radiological follow-up would have changed the outcome measure. [3]Downgraded one level for serious risk of bias due to confounding, it is possible that patients with a lower life expectancy were less likely to have been given therapeutic anticoagulation. [4]Downgraded one level for serious imprecision as therapeutic anticoagulation may have a different effect in patients with a chronic thrombosis or in patients with luminal narrowing without an actual filling defect and it was impossible to conduct separate subgroup-analysis. [5]Downgraded one level for serious imprecision, the 95% confidence interval was consistent with the possibility for benefit (which was predefined as a risk difference under -25% or over 25%).

DISCUSSION

In this systematic review and meta-analysis, 233 patients with AP and SVT from seven retrospective cohort studies were included. Of these patients, nearly half (47%) received therapeutic AC. Therapeutic AC was administered more often to patients with SpIV+PV+SMV thrombosis (72%) versus isolated SpIV (22%) or SMV thrombosis (0%). The results of current systematic review and meta-analysis of available evidence could not demonstrate that therapeutic AC improved rates of recanalization, formation of varices, collaterals or cavernoma and mortality compared to no therapeutic AC. The 95% confidence interval of haemorrhage also includes zero. This study mostly highlights the lack of high quality studies regarding this topic and emphasizes the need for further and higher quality data.

SVT is an increasingly recognized complication of AP, that as we show here, affect 7% of patients of which at least 89% suffer moderate severe or severe AP. SVT may lead

to portal hypertension and the formation of portosystemic collaterals (3). This altered vascular anatomy increases the risk of gastrointestinal haemorrhage, of which variceal haemorrhage is the most severe and potentially life-threatening event (28), and also has clinical implications for the treatment of moderate and severe AP (4).

Therapeutic AC in SVT is directed toward prevention of thrombosis progression, with recanalization being a hoped-for result, and recurrent VTE (5). A recent meta-analysis by Valeriani et al., involving 7668 patients with unselected SVT, found lower rates of thrombosis progression and higher rates of recanalization in patients receiving therapeutic AC (5% and 58%) compared to patient with no therapeutic AC (15% and 22%), while the incidence of recurrent VTE were similar in both groups (11% versus 14%) (29). It is noteworthy that this study mostly included patients with underlying liver cirrhosis, myeloproliferative neoplasms and solid cancer with or without thrombophilia. Compared to those latter risk factors, the hypercoagulable state of pancreatitis-induced SVT is related to inflammation of a temporary state (1, 3), and as a consequence, the benefits of AC therapy may be less profound. This hypothesis has been supported by a retrospective study that identified AP as a protective factor for insufficient recanalization (HR=0.3, 95% CI=0.2-0.7) in non-cirrhotic non-malignant PV thrombosis (30). In a meta-analysis including 252 AP patients with SVT, Hajibandeh et al. reported similar rates of recanalization in patients treated with AC therapy (32%) and without therapy (31%) (16). In contrast to the present study, this meta-analysis included only three retrospective cohort studies (n=91) (21, 22, 26) and included two conference abstracts (n=161) (31, 32), which have limited the risk-of-bias assessment. Further, it did not include a methods section or a discussion and consequently, key features of performing a systematic review and meta-analysis and its limitations did not become clear. The present study showed that the pooled recanalization rates of SVT in the setting of AP with therapeutic AC (36%) was slightly higher than without therapeutic AC (20%), for an absolute risk difference of 9%. Unfortunately, no information on thrombosis progression was reported in the included studies and due to limited reporting on recurrent VTE, no meta-analysis could be performed for these relevant outcomes. We were able to address the presence of varices, collaterals and cavernoma, as the development of collateral pathways is a sign of chronic SVT and hence, insufficient recanalization (33). In this study, the rates of varices/collaterals/cavernoma formation were substantial in both patients with therapeutic AC (51%) and without therapeutic AC (57%).

Intuitively, one might expect higher rates of haemorrhage in SVT patients treated with therapeutic AC. This is in line with previous studies showing that therapeutic AC increases the risk of haemorrhage in patients with SVT (6, 34). Of note, therapeutic AC might prevent thrombosis progression reducing portal pressure and

consequently, decreasing the risk of haemorrhage. This hypothesis has been supported by the previously mentioned meta-analysis by Valeriani et al., reporting lower rates of haemorrhage in therapeutic AC patients (9%) compared to untreated patients (16%) (29). However, patients with underlying AP appear to have additional risk of haemorrhage, as they often have local complications that, in the case of infected pancreatic necrosis or persistent symptoms, require endoscopic or percutaneous drainage (35). The previously mentioned meta-analysis by Hajibandeh et al. showed an increased rate of haemorrhage in AC patients (23%) compared to untreated patients (9%) (36). In this study, the absolute risk difference for haemorrhage of patients treated with full dose anticoagulation was 3%. Because possible selection bias we expect that this risk difference represents an underestimation: it is likely that a perceived high bleeding risk in AP patients influence the decision not to administer therapeutic AC in current practice, as more patients included in our analysis were left untreated (53%) when compared to data of patients from an unselected SVT population (26%) (29). The included studies mainly described haemorrhage at sites of pancreatic necrosis or fluid collections, haemorrhage in percutaneous drainage and haemorrhage from peptic ulcers in both groups. Only one study reported one case of variceal haemorrhage and three cases of haemorrhage from pseudoaneurysms in eight patients with haemorrhage complications, one of whom were treated with therapeutic AC (21).

The question that follows is whether SVT impact mortality in patients with AP. In a retrospective study of 4613 AP patients, the presence of VTE, including deep vein thrombosis (52%), pulmonary embolism (19%), SVT (16%) or a combination (13%), increased mortality compared with no VTE (27% vs. 13%) (37). Another study has shown worse survival of unselected patients with SVT than those with lower limb deep vein thrombosis or age- and sex-matched controls (34). Independent predictors for poor survival include PV thrombosis, multivessel involvement, underlying malignancy and older (34, 38, 39). In this study, we demonstrated an overall mortality rate of 6%, with comparable rates between patients with versus without therapeutic AC, which is much lower than reported in patients with severe AP (range between 20-40%) (7, 40). Due to lack of randomized controlled trials, our mortality rates are likely influenced by selection bias, for instance, patients with multivessel thrombosis or isolated PV thrombosis were more commonly treated than those with isolated SpIV or SMV thrombosis, leaving the effect of therapeutic AC on mortality unknown.

This systematic review and meta-analysis has several shortcomings. First, all included studies were cohort studies and probably underpowered to detect significant differences as only 233 patients with pancreatitis-induced SVT were analysed, of which 109 were treated with therapeutic AC. Second, the definition of SVT was not specified in four studies and there was heterogeneity between the other three studies. Two stud-

ies defined SVT as either luminal filling defect or luminal narrowing, whereas one study distinguished between actual thrombosis and narrowing. This may have led to overdiagnosis of SVT, as luminal narrowing may manifest secondary to extrinsic compression (i.e. enlarged pancreas, pancreatic fluid collections) in AP patients. Including overdiagnosed SVT may have led to underestimation of the effect of therapeutic AC. Third, none of the studies have classified the age of SVT at start of AC therapy into acute versus chronic. The time to detection is relevant since therapeutic AC probably has less effect in chronic SVT compared to SVT detected during clinical admission. Fourth, due to the observational designs, the decision regarding therapeutic AC was made per individual patient and therefore, it is reasonable to hypothesize that symptomatic patients with acute SVT were more likely to receive therapeutic AC compared to asymptomatic patients or patients with a high bleeding risk or lower life expectancy. This confounding by indication may have influenced the results. Fifth, five of the included studies did not have standardized radiological follow-up and consequently, the achievement of recanalization or the formation of varices, collaterals or cavernoma may be undetected in some patients. Sixth, the included studies were heterogenous in terms of SVT characteristics (i.e. anatomical localization and extent of thrombosis) and treatment characteristics (i.e. therapeutic AC agents and treatment duration), which limits between study comparability and due to limited data-availability, we could not perform regression analysis to examine these subset effects, which is a common limitation of study-level meta-analysis. Finally, the funnel plots with 7 included studies may not be meaningful, since the minimum required number of studies for assessment of publication bias is 10 (41, 42). Considering these limitations and the moderate risk of bias, the evidence should be rated as very low quality and recommendation should be considered as weak.

What are the clinical implications of our findings? In the current era with increasing rates of incidental venous thromboembolism secondary to the lower threshold for performing imaging alongside advancements in CT technology, evidence is accumulating that not all clots require AC treatment, such as is the case with subsegmental pulmonary embolism, especially in settings of high risk of bleeding (43, 44). Based on the currently available data, it remains unclear if therapeutic AC provides benefit to patients with AP and SVT. Although the current limited evidence does not allow for strict guideline recommendations, our findings do inform this decision making in clinical practice. Mostly, it urgently calls for a well-designed randomized controlled trial, ideally including (tertiary) centres with a relatively high incidence of SVT, considering the required sample size, to improve treatment and outcomes of patients with AP. This future trial should distinct between thrombosis and narrowing and between acute and chronic thrombosis. Furthermore, the type, dosage and duration

of treatment, (radiological) follow-up and outcomes need to be adequately defined and standardized.

CONCLUSION

Based on the currently available data, it remains unclear if therapeutic anticoagulation provides benefit to patients with acute pancreatitis and splanchnic vein thrombosis. These results are based on low quality data underlining the need for further higher quality studies.

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Supplementary file S1. Literature search

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(((”acute pancreatitis”[tw] OR ((”Pancreatitis”[mesh] OR ”pancreatitis”[tw]) AND (”Acute Disease”[mesh] OR ”acute*”[tw]))) AND (”Thrombosis”[Mesh] OR ”Thrombosis”[tw] OR ”Thrombo*”[tw] OR ”Thrombus”[tw] OR ”Thrombi”[tw] OR ”blood clot*”[tw] OR ”Budd-Chiari*”[tw] OR ”Postthrombo*”[tw] OR ”Retinal Vein Occlu*”[tw] OR ”Thrombophleb*”[tw] OR ”Lemierre Syndrome”[tw] OR ”DVT”[tw] OR ”vascular complicat*”[tw] OR ”Vascular Diseases”[mesh] OR ”Cardiovascular Diseases”[mesh]) AND (”Anticoagulants”[Mesh] OR ”Anticoagulants”[Pharmacological Action] OR ”Anticoagula*”[tw] OR ”Anti coagula*”[tw] OR ”(2S)-2-(4-(((3S)-1-acetimidoyl-3-pyrrolidinyl)oxy)phenyl)-3-(7-amidino-2-naphtyl) propanoic acid”[tw] OR ”1-(1-(3-((6-chloronaphthalen-2-yl)sulfonyl)-2-hydroxypropanoyl)piperidin-4-yl)tetrahydropyrimidin-2(1H)-one”[tw] OR ”1-(1-amino-7-isoquinolyl)-N-(2’-(aminosulfonyl)-1,1’-biphenyl-4-yl)-3-methyl-1H-pyrazole-5-carboxamide”[tw] OR ”1-(2,2-difluoroethyl)pyrrolidine-3,4-dicarboxylic acid 3-((5-chloropyridin-2-yl)amide) 4-((2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl) amide)”[tw] OR ”1-(3-(aminomethyl)phenyl)-N-(3-fluoro-2’-(methylsulfonyl) (1,1’-biphenyl)-4-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide”[tw] OR ”1-(3-aminobenzisoxazol-5’-yl)-3-trifluoromethyl-6-(2’-(3-hydroxy-N-pyrrolidinyl) methyl-(1,1’)-biphen-4-yl)-1,4,5,6-tetrahydropyrazolo-(3,4-c)-pyridin-7-one”[tw] OR ”2-(1-(3-((6-chloronaphthalen-2-yl)sulfonyl)propanoyl)piperidin-4-yl)-5-methyl-1,2-dihydro-3H-imidazo(1,5-c)imidazol-3-one”[tw] OR ”2-(4-(dimethylamino) benzoylamino)-5-methanesulfonylamino-N’-(4-methoxyphenyl)benzamide”[tw] OR ”2-(5-chlorothien-2-yl)-N-(1-(1-methyl-2-(morpholin-4-yl)-2-oxoethyl)-2-oxopyrrolidin-3-yl)ethenesulfonamide”[tw] OR ”2-carbamoyl-4-((6-chloronaphthalen-2-yl)sulfonyl)-1-((5-methyl-4,5,6,7-tetrahydrothiazolo(5,4-c)pyridin-2-yl) carbonyl)piperazine”[tw] OR ”3,3’-(3,5-difluoro-4-methyl-2,6-pyridinediylbis(oxy)) bis(benzenecarbox(imide)amide)”[tw] OR ”3-(4-(5-(2,6-dimethylpiperidin-1-yl)pentyl)-3-oxo-3,4-dihydroxyquinoxalin-2-yl)benzamidine”[tw] OR ”3-(4-(5-(2,6-dimethyltetrahydro-1(2H)-pyridinyl)pentyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)-1-benzenecarboximidamide”[tw] OR ”3-chloro-N-(4-chloro-2-(((5-chloro-2-pyridinyl)amino)carbonyl)-6-methoxyphenyl)-4-(((4,5-dihydro-2-oxazolyl)methylamino)methyl)-2-thiophenecarboxamide”[tw] OR ”3-chloro-N-(4-chloro-2-(((5-chloro-2-pyridinyl)amino)carbonyl)-6-methoxyphenyl)-4-((methylamino)methyl)-2-thiophenecarboxamide”[tw] OR ”4-((2-amidino-1,2,3,4-tetrahydroisoquinolin-7-yloxy)methyl)-1-(4-pyridinyl) piperidine-4-carboxylic acid monomethanesulfonate trihydrate”[tw] OR ”4-Hydroxycoumarins”[tw] OR ”5-chlorothiophene-2-carboxylic acid (2-(2-methyl-

3-(2-oxopyrrolidin-1-yl)benzenesulfonylamino)-3-(4-methylpiperazin-1-yl)-3-oxopropyl)amide"[tw] OR "6-(dimethylcarbamoyl)nicotinoyl guanidine"[tw] OR "6-chloromethyl-3-(2,5-dichlorophenoxycarbonyl)-2-benzopyrone"[tw] OR "6-methyl-1,2,3,5-tetrahydroimidazo(2,1-b)quinazolin-2-one hydrochloride"[tw] OR "Abciximab"[tw] OR "Acenocoumarol"[tw] OR "acid citrate dextrose"[tw] OR "alpha-(3-amidinylphenoxy)-2-bromo-N-(5-(pyrrolidin-1-ylcarbonyl)phenyl) phenylacetamide"[tw] OR "Ancrod"[tw] OR "antistasin"[tw] OR "Antithrombin III"[tw] OR "Antithrombin Proteins"[tw] OR "antivitamins K"[tw] OR "apixaban"[tw] OR "aprosulate"[tw] OR "ardeparin"[tw] OR "argatroban"[tw] OR "Becaplermin"[tw] OR "bemiparin"[tw] OR "beta 2-Glycoprotein I"[tw] OR "betrixaban"[tw] OR "bivalirudin"[tw] OR "Blood Coagulation Factor Inhibitors"[tw] OR "BMS 269223"[tw] OR "BnSO(2)-D-Arg-Gly-Arg-ketothiazole"[tw] OR "bromadiolone"[tw] OR "bromfenacoum"[tw] OR "calcium heparin"[tw] OR "certoparin"[tw] OR "chlorophacinone"[tw] OR "citrate phosphate dextrose"[tw] OR "Citric Acid"[tw] OR "clocoumarol"[tw] OR "coumachlor"[tw] OR "CPDA solutions"[tw] OR "Dabigatran"[tw] OR "Dalteparin"[tw] OR "danaparoid"[tw] OR "darexaban"[tw] OR "Dermatan Sulfate"[tw] OR "desirudin"[tw] OR "Dextrans"[tw] OR "Dicumarol"[tw] OR "difenacoum"[tw] OR "DPC 602"[tw] OR "Edetic Acid"[tw] OR "efegatran"[tw] OR "eisenstasin"[tw] OR "Enoxaparin"[tw] OR "Ethyl Biscoumacetate"[tw] OR "factor Xa, Glu-Gly-Arg-"[tw] OR "ferulic acid"[tw] OR "Fibrin Fibrinogen Degradation Products"[tw] OR "fibrinogen fragment X"[tw] OR "fluindione"[tw] OR "Fondaparinux"[tw] OR "fucoidan"[tw] OR "FX 2212"[tw] OR "Gabexate"[tw] OR "glucuronyl glucosamine glycan sulfate"[tw] OR "Heparin"[tw] OR "Heparin Cofactor II"[tw] OR "Heparin, Low-Molecular-Weight"[tw] OR "Heparinoids"[tw] OR "Hirudins"[tw] OR "HY023016"[tw] OR "idrabiotaparinux"[tw] OR "idraparinux"[tw] OR "inogatran"[tw] OR "isoleucyl-glutamyl-glycyl-arginine chloromethyl ketone"[tw] OR "ITF 1331"[tw] OR "lamifiban"[tw] OR "laminaran"[tw] OR "lefaxin"[tw] OR "lepirudin"[tw] OR "lipoprotein-associated coagulation inhibitor"[tw] OR "lufaxin protein, Lutzomyia longipalpis"[tw] OR "melagatran"[tw] OR "moxicoumone"[tw] OR "N(2)-(4-(dimethylamino)benzoyl)-4-hydroxy-N(1)-(4-methoxybenzoyl)-1,2-benzenediamine"[tw] OR "N(alpha)-(2-naphthylsulfonylglycyl)-4-amidinophenylalanine piperidide"[tw] OR "N-(4-(1-(acetimidoyl)piperidin-4-yloxy)-3-carbamoylphenyl)-N-(3-(3-amidinophenyl)-2-fluoro-2-propenyl)sulfamoylacetic acid"[tw] OR "N-(4-chlorophenyl)-N-(2-fluoro-4-(2-oxopyridin-1(2H)-yl) phenyl)-4-methoxypyrrolidiine-1,2-dicarboxamide"[tw] OR "Nadroparin"[tw] OR "nafamostat"[tw] OR "nitrophorin"[tw] OR "otamixaban"[tw] OR "parnaparin"[tw] OR "PD0313052"[tw] OR "PENTA"[tw] OR "Pentosan Sulfuric Polyester"[tw] OR "Phenindione"[tw] OR "Phenprocoumon"[tw] OR "plumbagin"[tw] OR "Protein C"[tw] OR "Protein S"[tw] OR "protocatechualdehyde"[tw] OR "pyragrel"[tw] OR

”reviparin”[tw] OR ”Rivaroxaban”[tw] OR ”RPR 120844”[tw] OR ”RPR 130737”[tw] OR ”RPR 208566”[tw] OR ”RPR 209685”[tw] OR ”RWJ 445167”[tw] OR ”SDZ MTH 958”[tw] OR ”SE 170”[tw] OR ”SEL 2711”[tw] OR ”SF 324”[tw] OR ”Sodium Citrate”[tw] OR ”SV-66 protein, Simulium vittatum”[tw] OR ”tanshinone”[tw] OR ”therostasin protein, Theromyzon tessulatum”[tw] OR ”tick anticoagulant peptide”[tw] OR ”Tinzaparin”[tw] OR ”tocopherylquinone”[tw] OR ”troxerutin”[tw] OR ”Warfarin”[tw] OR ”WX-FX4 compound”[tw] OR ”ximelagatran”[tw] OR ”YM 60828”[tw] OR ”ZK 805412”[tw] OR ”ZK 806299”[tw])) OR ((”acute pancreatitis”[ti] OR ((”Pancreatitis”[majr] OR ”pancreatitis”[ti]) AND (”Acute Disease”[majr] OR ”acute*”[ti]))) AND (”Thrombosis”[Mesh] OR ”Thrombosis”[tw] OR ”Thrombo*”[tw] OR ”Thrombus”[tw] OR ”Thrombi”[tw] OR ”blood clot*”[tw] OR ”Budd-Chiari*”[tw] OR ”Postthrombo*”[tw] OR ”Retinal Vein Occlu*”[tw] OR ”Thrombophleb*”[tw] OR ”Lemierre Syndrome”[tw] OR ”DVT”[tw] OR ”vascular complicat*”[tw]))) NOT (”Animals”[mesh] NOT ”Humans”[mesh]) AND english[la]

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(((*”acute pancreatitis”/ OR ”acute pancreatitis”.ti,ab OR ((exp *”Pancreatitis”/ OR ”pancreatitis”.ti,ab) AND (*”Acute Disease”/ OR ”acute*”.ti,ab))) AND (exp *”Thrombosis”/ OR ”Thrombosis”.ti,ab OR ”Thrombo*”.ti,ab OR ”Thrombus”.ti,ab OR ”Thrombi”.ti,ab OR ”blood clot*”.ti,ab OR ”Budd-Chiari*”.ti,ab OR ”Postthrombo*”.ti,ab OR ”Retinal Vein Occlu*”.ti,ab OR ”Thrombophleb*”.ti,ab OR ”Lemierre Syndrome”.ti,ab OR ”DVT”.ti,ab OR ”vascular complicat*”.ti,ab OR exp *”Vascular Disease”/) AND (exp *”Anticoagulant Agent”/ OR ”Anticoagula*”.ti,ab OR ”Anti coagula*”.ti,ab OR ”(2S)-2-(4-(((3S)-1-acetimidoyl-3-pyrrolidinyl)oxy)phenyl)-3-(7-amidino-2-naphtyl)propanoic acid”.ti,ab OR ”1-(1-(3-((6-chloronaphthalen-2-yl)sulfonyl)-2-hydroxypropanoyl)piperidin-4-yl) tetrahydropyrimidin-2(1H)-one”.ti,ab OR ”1-(1-amino-7-isoquinolyl)-N-(2’-(aminosulfonyl)-1,1’-biphenyl-4-yl)-3-methyl-1H-pyrazole-5-carboxamide”.ti,ab OR ”1-(2,2-difluoroethyl)pyrrolidine-3,4-dicarboxylic acid 3-((5-chloropyridin-2-yl)amide) 4-((2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl)amide)”.ti,ab OR ”1-(3-(aminomethyl)phenyl)-N-(3-fluoro-2’-(methylsulfonyl) (1,1’-biphenyl)-4-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide”.ti,ab OR ”1-(3-aminobenzisoxazol-5’-yl)-3-trifluoromethyl-6-(2’-(3-hydroxy-N-pyrrolidinyl) methyl-(1,1’)-biphen-4-yl)-1,4,5,6-tetrahydropyrazolo-(3,4-c)-pyridin-7-one”.ti,ab OR ”2-(1-(3-((6-chloronaphthalen-2-yl)sulfonyl)propanoyl)piperidin-4-yl)-5-methyl-1,2-dihydro-3H-imidazo(1,5-c)imidazol-3-one”.ti,ab OR ”2-(4-(dimethylamino)benzoylamino)-5-methanesulfonylamino-N’-(4-methoxyphenyl) benzamide”.ti,ab OR ”2-(5-chlorothien-2-yl)-N-(1-(1-methyl-2-(morpholin-4-yl)-2-oxoethyl)-2-oxopyrrolidin-3-yl)ethenesulfonamide”.ti,ab OR ”2-carbamoyl-4-((6-

chloronaphthalen-2-yl)sulfonyl)-1-((5-methyl-4,5,6,7-tetrahydrothiazolo(5,4-c) pyridin-2-yl)carbonyl)piperazine".ti,ab OR "3,3'-(3,5-difluoro-4-methyl-2,6-pyridinediylbis(oxy))bis(benzenecarbox(imide)amide)".ti,ab OR "3-(4-(5-(2,6-dimethylpiperidin-1-yl)pentyl)-3-oxo-3,4-dihydroxyquinoxalin-2-yl)benzamidine". ti,ab OR "3-(4-(5-(2,6-dimethyltetrahydro-1(2H)-pyridinyl)pentyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)-1-benzenecarboximidamide".ti,ab OR "3-chloro-N-(4-chloro-2-(((5-chloro-2-pyridinyl)amino)carbonyl)-6-methoxyphenyl)-4-(((4,5-dihydro-2-oxazolyl)methylamino)methyl)-2-thiophenecarboxamide". ti,ab OR "3-chloro-N-(4-chloro-2-(((5-chloro-2-pyridinyl)amino)carbonyl)-6-methoxyphenyl)-4-((methylamino)methyl)-2-thiophenecarboxamide".ti,ab OR "4-((2-amidino-1,2,3,4-tetrahydroisoquinolin-7-yloxy)methyl)-1-(4-pyridinyl) piperidine-4-carboxylic acid monomethanesulfonate trihydrate".ti,ab OR "4-Hydroxycoumarins".ti,ab OR "5-chlorothiophene-2-carboxylic acid (2-(2-methyl-3-(2-oxopyrrolidin-1-yl)benzenesulfonylamino)-3-(4-methylpiperazin-1-yl)-3-oxopropyl)amide".ti,ab OR "6-(dimethylcarbamoyl)nicotinoyl guanidine".ti,ab OR "6-chloromethyl-3-(2,5-dichlorophenoxycarbonyl)-2-benzopyrone".ti,ab OR "6-methyl-1,2,3,5-tetrahydroimidazo(2,1-b)quinazolin-2-one hydrochloride".ti,ab OR "Abciximab".ti,ab OR "Acenocoumarol".ti,ab OR "acid citrate dextrose".ti,ab OR "alpha-(3-amidinylphenoxy)-2-bromo-N-(5-(pyrrolidin-1-ylcarbonyl)phenyl) phenylacetamide".ti,ab OR "Ancrod".ti,ab OR "antistasin".ti,ab OR "Antithrombin III".ti,ab OR "Antithrombin Proteins".ti,ab OR "antivitamins K".ti,ab OR "apixaban".ti,ab OR "aprosulate".ti,ab OR "ardeparin".ti,ab OR "argatroban".ti,ab OR "Becaplermin".ti,ab OR "bemiparin".ti,ab OR "beta 2-Glycoprotein I".ti,ab OR "betrixaban".ti,ab OR "bivalirudin".ti,ab OR "Blood Coagulation Factor Inhibitors". ti,ab OR "BMS 269223".ti,ab OR "BnSO(2)-D-Arg-Gly-Arg-ketothiazole".ti,ab OR "bromadiolone".ti,ab OR "bromfenacoum".ti,ab OR "calcium heparin".ti,ab OR "certoparin".ti,ab OR "chlorophacinone".ti,ab OR "citrate phosphate dextrose".ti,ab OR "Citric Acid".ti,ab OR "clocoumarol".ti,ab OR "coumachlor".ti,ab OR "CPDA solutions".ti,ab OR "Dabigatran".ti,ab OR "Dalteparin".ti,ab OR "danaparoid".ti,ab OR "darexaban".ti,ab OR "Dermatan Sulfate".ti,ab OR "desirudin".ti,ab OR "Dextrans". ti,ab OR "Dicumarol".ti,ab OR "difenacoum".ti,ab OR "DPC 602".ti,ab OR "Edetic Acid".ti,ab OR "efegatran".ti,ab OR "eisenstasin".ti,ab OR "Enoxaparin".ti,ab OR "Ethyl Biscoumacetate".ti,ab OR "factor Xa, Glu-Gly-Arg-".ti,ab OR "ferulic acid". ti,ab OR "Fibrin Fibrinogen Degradation Products".ti,ab OR "fibrinogen fragment X".ti,ab OR "fluindione".ti,ab OR "Fondaparinux".ti,ab OR "fucoidan".ti,ab OR "FX 2212".ti,ab OR "Gabexate".ti,ab OR "glucuronyl glucosamine glycan sulfate". ti,ab OR "Heparin".ti,ab OR "Heparin Cofactor II".ti,ab OR "Heparin, Low-Molecular-Weight".ti,ab OR "Heparinoids".ti,ab OR "Hirudins".ti,ab OR "HY023016". ti,ab OR "idrabiotaparinux".ti,ab OR "idraparinux".ti,ab OR "inogatran".ti,ab OR "isoleucyl-glutamyl-glycyl-arginine chloromethyl ketone".ti,ab OR "ITF 1331".ti,ab

OR ”lamifiban”.ti,ab OR ”laminaran”.ti,ab OR ”lefaxin”.ti,ab OR ”lepirudin”.ti,ab OR ”lipoprotein-associated coagulation inhibitor”.ti,ab OR ”lufaxin protein, Lutzomyia longipalpis”.ti,ab OR ”melagatran”.ti,ab OR ”moxicoumone”.ti,ab OR ”N(2)-(4-(dimethylamino)benzoyl)-4-hydroxy-N(1)-(4-methoxybenzoyl)-1,2-benzenediamine”.ti,ab OR ”N(alpha)-(2-naphthylsulfonylglycyl)-4-amidinophenylalanine piperidide”.ti,ab OR ”N-(4-(1-(acetimidoyl)piperidin-4-yloxy)-3-carbamoylphenyl)-N-(3-(3-amidinophenyl)-2-fluoro-2-propenyl)sulfamoylacetic acid”.ti,ab OR ”N-(4-chlorophenyl)-N-(2-fluoro-4-(2-oxopyridin-1(2H)-yl)phenyl)-4-methoxypyrrolidiine-1,2-dicarboxamide”.ti,ab OR ”Nadroparin”.ti,ab OR ”nafamostat”.ti,ab OR ”nitrophorin”.ti,ab OR ”otamixaban”.ti,ab OR ”parnaparin”.ti,ab OR ”PD0313052”.ti,ab OR ”PENTA”.ti,ab OR ”Pentosan Sulfuric Polyester”.ti,ab OR ”Phenindione”.ti,ab OR ”Phenprocoumon”.ti,ab OR ”plumbagin”.ti,ab OR ”Protein C”.ti,ab OR ”Protein S”.ti,ab OR ”protocatechualdehyde”.ti,ab OR ”pyragrel”.ti,ab OR ”reviparin”.ti,ab OR ”Rivaroxaban”.ti,ab OR ”RPR 120844”.ti,ab OR ”RPR 130737”.ti,ab OR ”RPR 208566”.ti,ab OR ”RPR 209685”.ti,ab OR ”RWJ 445167”.ti,ab OR ”SDZ MTH 958”.ti,ab OR ”SE 170”.ti,ab OR ”SEL 2711”.ti,ab OR ”SF 324”.ti,ab OR ”Sodium Citrate”.ti,ab OR ”SV-66 protein, Simulium vittatum”.ti,ab OR ”tanshinone”.ti,ab OR ”therostasin protein, Theromyzon tessulatum”.ti,ab OR ”tick anticoagulant peptide”.ti,ab OR ”Tinzaparin”.ti,ab OR ”tocopherylquinone”.ti,ab OR ”troxerutin”.ti,ab OR ”Warfarin”.ti,ab OR ”WX-FX4 compound”.ti,ab OR ”ximelagatran”.ti,ab OR ”YM 60828”.ti,ab OR ”ZK 805412”.ti,ab OR ”ZK 806299”.ti,ab)) OR ((*”acute pancreatitis”/ OR ”acute pancreatitis”.ti OR ((exp *”Pancreatitis”/ OR ”pancreatitis”.ti) AND (*”Acute Disease”/ OR ”acute*”.ti))) AND (exp *”Thrombosis”/ OR ”Thrombosis”.ti,ab OR ”Thrombo*”.ti,ab OR ”Thrombus”.ti,ab OR ”Thrombi”.ti,ab OR ”blood clot*”.ti,ab OR ”Budd-Chiari*”.ti,ab OR ”Postthrombo*”.ti,ab OR ”Retinal Vein Occlu*”.ti,ab OR ”Thrombophleb*”.ti,ab OR ”Lemierre Syndrome”.ti,ab OR ”DVT”.ti,ab OR ”vascular complicat*”.ti,ab))) NOT (exp ”Animals”/ NOT exp ”Humans”/) AND english.la

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((ts=(”acute pancreatitis” OR ”acute pancreatitis” OR ((”Pancreatitis” OR ”pancreatitis”) AND (”Acute Disease” OR ”acute*”))) AND ts=(”Thrombosis” OR ”Thrombosis” OR ”Thrombo*” OR ”Thrombus” OR ”Thrombi” OR ”blood clot*” OR ”Budd-Chiari*” OR ”Postthrombo*” OR ”Retinal Vein Occlu*” OR ”Thrombophleb*” OR ”Lemierre Syndrome” OR ”DVT” OR ”vascular complicat*” OR ”Vascular Disease”) AND ts=(”Anticoagulant Agent” OR ”Anticoagula*” OR ”Anti coagula*” OR ”(2S)-2-(4-(((3S)-1-acetimidoyl-3-pyrrolidinyl)oxy)phenyl)-3-(7-amidino-2-naphtyl)propanoic acid” OR ”1-(1-(3-((6-chloronaphthalen-2-yl)sulfonyl)-2-hydroxypropanoyl)piperidin-4-yl)tetrahydropyrimidin-2(1H)-one” OR

”1-(1-amino-7-isoquinolyl)-N-(2’-(aminosulfonyl)-1,1’-biphenyl-4-yl)-3-methyl-1H-pyrazole-5-carboxamide” OR ”1-(2,2-difluoroethyl)pyrrolidine-3,4-dicarboxylic acid 3-((5-chloropyridin-2-yl)amide) 4-((2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl)amide)” OR ”1-(3-(aminomethyl)phenyl)-N-(3-fluoro-2’-(methylsulfonyl)(1,1’-biphenyl)-4-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide” OR ”1-(3-aminobenzisoxazol-5’-yl)-3-trifluoromethyl-6-(2’-(3-hydroxy-N-pyrrolidinyl)methyl-(1,1’)-biphen-4-yl)-1,4,5,6-tetrahydropyrazolo-(3,4-c)-pyridin-7-one” OR ”2-(1-(3-((6-chloronaphthalen-2-yl)sulfonyl)propanoyl)piperidin-4-yl)-5-methyl-1,2-dihydro-3H-imidazo(1,5-c)imidazol-3-one” OR ”2-(4-(dimethylamino)benzoylamino)-5-methanesulfonylamino-N’-(4-methoxyphenyl)benzamide” OR ”2-(5-chlorothien-2-yl)-N-(1-(1-methyl-2-(morpholin-4-yl)-2-oxoethyl)-2-oxopyrrolidin-3-yl)ethenesulfonamide” OR ”2-carbamoyl-4-((6-chloronaphthalen-2-yl)sulfonyl)-1-((5-methyl-4,5,6,7-tetrahydrothiazolo(5,4-c)pyridin-2-yl)carbonyl)piperazine” OR ”3,3’-(3,5-difluoro-4-methyl-2,6-pyridinediylbis(oxy))bis(benzenecarbox(imide)amide)” OR ”3-(4-(5-(2,6-dimethylpiperidin-1-yl)pentyl)-3-oxo-3,4-dihydroxyquinoxalin-2-yl)benzamidine” OR ”3-(4-(5-(2,6-dimethyltetrahydro-1(2H)-pyridinyl)pentyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)-1-benzenecarboximidamide” OR ”3-chloro-N-(4-chloro-2-(((5-chloro-2-pyridinyl)amino)carbonyl)-6-methoxyphenyl)-4-(((4,5-dihydro-2-oxazolyl)methylamino)methyl)-2-thiophenecarboxamide” OR ”3-chloro-N-(4-chloro-2-(((5-chloro-2-pyridinyl)amino)carbonyl)-6-methoxyphenyl)-4-((methylamino)methyl)-2-thiophenecarboxamide” OR ”4-((2-amidino-1,2,3,4-tetrahydroisoquinolin-7-yloxy)methyl)-1-(4-pyridinyl)piperidine-4-carboxylic acid monomethanesulfonate trihydrate” OR ”4-Hydroxycoumarins” OR ”5-chlorothiophene-2-carboxylic acid (2-(2-methyl-3-(2-oxopyrrolidin-1-yl)benzenesulfonylamino)-3-(4-methylpiperazin-1-yl)-3-oxopropyl)amide” OR ”6-(dimethylcarbamoyl)nicotinoyl guanidine” OR ”6-chloromethyl-3-(2,5-dichlorophenoxycarbonyl)-2-benzopyrone” OR ”6-methyl-1,2,3,5-tetrahydroimidazo(2,1-b)quinazolin-2-one hydrochloride” OR ”Abciximab” OR ”Acenocoumarol” OR ”acid citrate dextrose” OR ”alpha-(3-amidinylphenoxy)-2-bromo-N-(5-(pyrrolidin-1-ylcarbonyl)phenyl)phenylacetamide” OR ”Ancrod” OR ”antistasin” OR ”Antithrombin III” OR ”Antithrombin Proteins” OR ”antivitamins K” OR ”apixaban” OR ”aprosulate” OR ”ardeparin” OR ”argatroban” OR ”Becaplermin” OR ”bemiparin” OR ”beta 2-Glycoprotein I” OR ”betrixaban” OR ”bivalirudin” OR ”Blood Coagulation Factor Inhibitors” OR ”BMS 269223” OR ”BnSO(2)-D-Arg-Gly-Arg-ketothiazole” OR ”bromadiolone” OR ”bromfenacoum” OR ”calcium heparin” OR ”certoparin” OR ”chlorophacinone” OR ”citrate phosphate dextrose” OR ”Citric Acid” OR ”clocoumarol” OR ”coumachlor” OR ”CPDA solutions” OR ”Dabigatran” OR ”Dalteparin” OR ”danaparoid” OR ”darexaban” OR ”Dermatan Sulfate” OR ”desirudin” OR ”Dextrans” OR ”Dicumarol” OR ”difenacoum” OR ”DPC 602” OR ”Edetic Acid” OR ”efegatran” OR ”eisenstasin” OR ”Enoxaparin” OR

”Ethyl Biscoumacetate” OR ”factor Xa, Glu-Gly-Arg-” OR ”ferulic acid” OR ”Fibrin Fibrinogen Degradation Products” OR ”fibrinogen fragment X” OR ”fluindione” OR ”Fondaparinux” OR ”fucoidan” OR ”FX 2212” OR ”Gabexate” OR ”glucuronyl glucosamine glycan sulfate” OR ”Heparin” OR ”Heparin Cofactor II” OR ”Heparin, Low-Molecular-Weight” OR ”Heparinoids” OR ”Hirudins” OR ”HY023016” OR ”idrabiotaparinux” OR ”idraparinux” OR ”inogatran” OR ”isoleucyl-glutamyl-glycyl-arginine chloromethyl ketone” OR ”ITF 1331” OR ”lamifiban” OR ”laminaran” OR ”lefaxin” OR ”lepirudin” OR ”lipoprotein-associated coagulation inhibitor” OR ”lufaxin protein, Lutzomyia longipalpis” OR ”melagatran” OR ”moxicoumone” OR ”N(2)-(4-(dimethylamino)benzoyl)-4-hydroxy-N(1)-(4-methoxybenzoyl)-1,2-benzenediamine” OR ”N(alpha)-(2-naphthylsulfonylglycyl)-4-amidinophenylalanine piperidide” OR ”N-(4-(1-(acetimidoyl)piperidin-4-yloxy)-3-carbamoylphenyl)-N-(3-(3-amidinophenyl)-2-fluoro-2-propenyl)sulfamoylacetic acid” OR ”N-(4-chlorophenyl)-N-(2-fluoro-4-(2-oxopyridin-1(2H)-yl)phenyl)-4-methoxypyrrolidine-1,2-dicarboxamide” OR ”Nadroparin” OR ”nafamostat” OR ”nitrophorin” OR ”otamixaban” OR ”parnaparin” OR ”PD0313052” OR ”PENTA” OR ”Pentosan Sulfuric Polyester” OR ”Phenindione” OR ”Phenprocoumon” OR ”plumbagin” OR ”Protein C” OR ”Protein S” OR ”protocatechualdehyde” OR ”pyragrel” OR ”reviparin” OR ”Rivaroxaban” OR ”RPR 120844” OR ”RPR 130737” OR ”RPR 208566” OR ”RPR 209685” OR ”RWJ 445167” OR ”SDZ MTH 958” OR ”SE 170” OR ”SEL 2711” OR ”SF 324” OR ”Sodium Citrate” OR ”SV-66 protein, Simulium vittatum” OR ”tanshinone” OR ”therostasin protein, Theromyzon tessulatum” OR ”tick anticoagulant peptide” OR ”Tinzaparin” OR ”tocopherylquinone” OR ”troxerutin” OR ”Warfarin” OR ”WX-FX4 compound” OR ”ximelagatran” OR ”YM 60828” OR ”ZK 805412” OR ”ZK 806299”)) OR (ti=(”acute pancreatitis” OR ”acute pancreatitis” OR ((”Pancreatitis” OR ”pancreatitis”) AND (”Acute Disease” OR ”acute*”))) AND ts=(”Thrombosis” OR ”Thrombosis” OR ”Thrombo*” OR ”Thrombus” OR ”Thrombi” OR ”blood clot*” OR ”Budd-Chiari*” OR ”Postthrombo*” OR ”Retinal Vein Occlu*” OR ”Thrombophleb*” OR ”Lemierre Syndrome” OR ”DVT” OR ”vascular complicat*”))) AND la=english **NOT ti=(”veterinary” OR ”rabbit” OR ”rabbits” OR ”animal” OR ”animals” OR ”mouse” OR ”mice” OR ”rodent” OR ”rodents” OR ”rat” OR ”rats” OR ”pig” OR ”pigs” OR ”porcine” OR ”horse” OR ”horses” OR ”equine” OR ”cow” OR ”cows” OR ”bovine” OR ”goat” OR ”goats” OR ”sheep” OR ”ovine” OR ”canine” OR ”dog” OR ”dogs” OR ”feline” OR ”cat” OR ”cats”)**

Cochrane

(((”acute pancreatitis” OR ”acute pancreatitis” OR ((”Pancreatitis” OR ”pancreatitis”) AND (”Acute Disease” OR ”acute*”))) AND (”Thrombosis” OR ”Thrombosis”

OR "Thrombo*" OR "Thrombus" OR "Thrombi" OR "blood clot*" OR "Budd-Chiari*" OR "Postthrombo*" OR "Retinal Vein Occlu*" OR "Thrombophleb*" OR "Lemierre Syndrome" OR "DVT" OR "vascular complicat*" OR "Vascular Disease" OR vascular) AND ("Anticoagulant Agent" OR "Anticoagula*" OR "Anti coagula*" OR "(2S)-2-(4-(((3S)-1-acetimidoyl-3-pyrrolidinyl)oxy)phenyl)-3-(7-amidino-2-naphtyl)propanoic acid" OR "1-(1-(3-((6-chloronaphthalen-2-yl) sulfonyl)-2-hydroxypropanoyl)piperidin-4-yl)tetrahydropyrimidin-2(1H)-one" OR "1-(1-amino-7-isoquinolyl)-N-(2'-(aminosulfonyl)-1,1'-biphenyl-4-yl)-3-methyl-1H-pyrazole-5-carboxamide" OR "1-(2,2-difluoroethyl)pyrrolidine-3,4-dicarboxylic acid 3-((5-chloropyridin-2-yl)amide) 4-((2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl)amide)" OR "1-(3-(aminomethyl)phenyl)-N-(3-fluoro-2'-(methylsulfonyl) (1,1'-biphenyl)-4-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide" OR "1-(3-aminobenzisoxazol-5'-yl)-3-trifluoromethyl-6-(2'-(3-hydroxy-N-pyrrolidinyl) methyl-(1,1')-biphen-4-yl)-1,4,5,6-tetrahydropyrazolo-(3,4-c)-pyridin-7-one" OR "2-(1-(3-((6-chloronaphthalen-2-yl)sulfonyl)propanoyl)piperidin-4-yl)-5-methyl-1,2-dihydro-3H-imidazo(1,5-c)imidazol-3-one" OR "2-(4-(dimethylamino) benzoylamino)-5-methanesulfonylamino-N'-(4-methoxyphenyl)benzamide" OR "2-(5-chlorothien-2-yl)-N-(1-(1-methyl-2-(morpholin-4-yl)-2-oxoethyl)-2-oxopyrrolidin-3-yl)ethenesulfonamide" OR "2-carbamoyl-4-((6-chloronaphthalen-2-yl)sulfonyl)-1-((5-methyl-4,5,6,7-tetrahydrothiazolo(5,4-c)pyridin-2-yl) carbonyl)piperazine" OR "3,3'-(3,5-difluoro-4-methyl-2,6-pyridinediylbis(oxy)) bis(benzenecarbox(imide)amide)" OR "3-(4-(5-(2,6-dimethylpiperidin-1-yl) pentyl)-3-oxo-3,4-dihydroxyquinoxalin-2-yl)benzamidine" OR "3-(4-(5-(2,6-dimethyltetrahydro-1(2H)-pyridinyl)pentyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)-1-benzenecarboximidamide" OR "3-chloro-N-(4-chloro-2-(((5-chloro-2-pyridinyl)amino)carbonyl)-6-methoxyphenyl)-4-(((4,5-dihydro-2-oxazolyl) methylamino)methyl)-2-thiophenecarboxamide" OR "3-chloro-N-(4-chloro-2-(((5-chloro-2-pyridinyl)amino)carbonyl)-6-methoxyphenyl)-4-((methylamino)methyl)-2-thiophenecarboxamide" OR "4-((2-amidino-1,2,3,4-tetrahydroisoquinolin-7-yloxy)methyl)-1-(4-pyridinyl)piperidine-4-carboxylic acid monomethanesulfonate trihydrate" OR "4-Hydroxycoumarins" OR "5-chlorothiophene-2-carboxylic acid (2-(2-methyl-3-(2-oxopyrrolidin-1-yl)benzenesulfonylamino)-3-(4-methylpiperazin-1-yl)-3-oxopropyl)amide" OR "6-(dimethylcarbamoyl)nicotinoyl guanidine" OR "6-chloromethyl-3-(2,5-dichlorophenoxycarbonyl)-2-benzopyrone" OR "6-methyl-1,2,3,5-tetrahydroimidazo(2,1-b)quinazolin-2-one hydrochloride" OR "Abciximab" OR "Acenocoumarol" OR "acid citrate dextrose" OR "alpha-(3-amidinylphenoxy)-2-bromo-N-(5-(pyrrolidin-1-ylcarbonyl)phenyl)phenylacetamide" OR "Ancrod" OR "antistasin" OR "Antithrombin III" OR "Antithrombin Proteins" OR "antivitamins K" OR "apixaban" OR "aprosulate" OR "ardeparin" OR "argatroban" OR "Becaplermin" OR "bemiparin" OR "beta 2-Glycoprotein I" OR "betrixaban" OR

”bivalirudin” OR ”Blood Coagulation Factor Inhibitors” OR ”BMS 269223” OR ”BnSO(2)-D-Arg-Gly-Arg-ketothiazole” OR ”bromadiolone” OR ”bromfenacoum” OR ”calcium heparin” OR ”certoparin” OR ”chlorophacinone” OR ”citrate phosphate dextrose” OR ”Citric Acid” OR ”clocoumarol” OR ”coumachlor” OR ”CPDA solutions” OR ”Dabigatran” OR ”Dalteparin” OR ”danaparoid” OR ”darexaban” OR ”Dermatan Sulfate” OR ”desirudin” OR ”Dextrans” OR ”Dicumarol” OR ”difenacoum” OR ”DPC 602” OR ”Edetic Acid” OR ”efegatran” OR ”eisenstasin” OR ”Enoxaparin” OR ”Ethyl Biscoumacetate” OR ”factor Xa, Glu-Gly-Arg-” OR ”ferulic acid” OR ”Fibrin Fibrinogen Degradation Products” OR ”fibrinogen fragment X” OR ”fluindione” OR ”Fondaparinux” OR ”fucoidan” OR ”FX 2212” OR ”Gabexate” OR ”glucuronyl glucosamine glycan sulfate” OR ”Heparin” OR ”Heparin Cofactor II” OR ”Heparin, Low-Molecular-Weight” OR ”Heparinoids” OR ”Hirudins” OR ”HY023016” OR ”idrabiotaparinux” OR ”idraparinux” OR ”inogatran” OR ”isoleucyl-glutamyl-glycyl-arginine chloromethyl ketone” OR ”ITF 1331” OR ”lamifiban” OR ”laminaran” OR ”lefaxin” OR ”lepirudin” OR ”lipoprotein-associated coagulation inhibitor” OR ”lufaxin protein, Lutzomyia longipalpis” OR ”melagatran” OR ”moxicoumone” OR ”N(2)-(4-(dimethylamino)benzoyl)-4-hydroxy-N(1)-(4-methoxybenzoyl)-1,2-benzenediamine” OR ”N(alpha)-(2-naphthylsulfonylglycyl)-4-amidinophenylalanine piperidide” OR ”N-(4-(1-(acetimidoyl)piperidin-4-yloxy)-3-carbamoylphenyl)-N-(3-(3-amidinophenyl)-2-fluoro-2-propenyl)sulfamoylacetic acid” OR ”N-(4-chlorophenyl)-N-(2-fluoro-4-(2-oxopyridin-1(2H)-yl)phenyl)-4-methoxypyrrolidiine-1,2-dicarboxamide” OR ”Nadroparin” OR ”nafamostat” OR ”nitrophorin” OR ”otamixaban” OR ”parnaparin” OR ”PD0313052” OR ”PENTA” OR ”Pentosan Sulfuric Polyester” OR ”Phenindione” OR ”Phenprocoumon” OR ”plumbagin” OR ”Protein C” OR ”Protein S” OR ”protocatechualdehyde” OR ”pyragrel” OR ”reviparin” OR ”Rivaroxaban” OR ”RPR 120844” OR ”RPR 130737” OR ”RPR 208566” OR ”RPR 209685” OR ”RWJ 445167” OR ”SDZ MTH 958” OR ”SE 170” OR ”SEL 2711” OR ”SF 324” OR ”Sodium Citrate” OR ”SV-66 protein, Simulium vittatum” OR ”tanshinone” OR ”therostasin protein, Theromyzon tessulatum” OR ”tick anticoagulant peptide” OR ”Tinzaparin” OR ”tocopherylquinone” OR ”troxerutin” OR ”Warfarin” OR ”WX-FX4 compound” OR ”ximelagatran” OR ”YM 60828” OR ”ZK 805412” OR ”ZK 806299”)):ti,ab,kw OR ((”acute pancreatitis” OR ”acute pancreatitis” OR ((”Pancreatitis” OR ”pancreatitis”) AND (”Acute Disease” OR ”acute*”))):ti,ab,kw AND (”Thrombosis” OR ”Thrombosis” OR ”Thrombo*” OR ”Thrombus” OR ”Thrombi” OR ”blood clot*” OR ”Budd-Chiari*” OR ”Postthrombo*” OR ”Retinal Vein Occlu*” OR ”Thrombophleb*” OR ”Lemierre Syndrome” OR ”DVT” OR ”vascular complicat*” OR vascular):ti)) AND la=english **NOT ti=(”veterinary” OR ”rabbit” OR ”rabbits” OR ”animal” OR ”animals” OR ”mouse” OR ”mice” OR ”rodent” OR ”rodents” OR ”rat” OR ”rats” OR ”pig” OR ”pigs” OR ”porcine” OR ”horse” OR ”horses” OR ”equine” OR ”cow”**

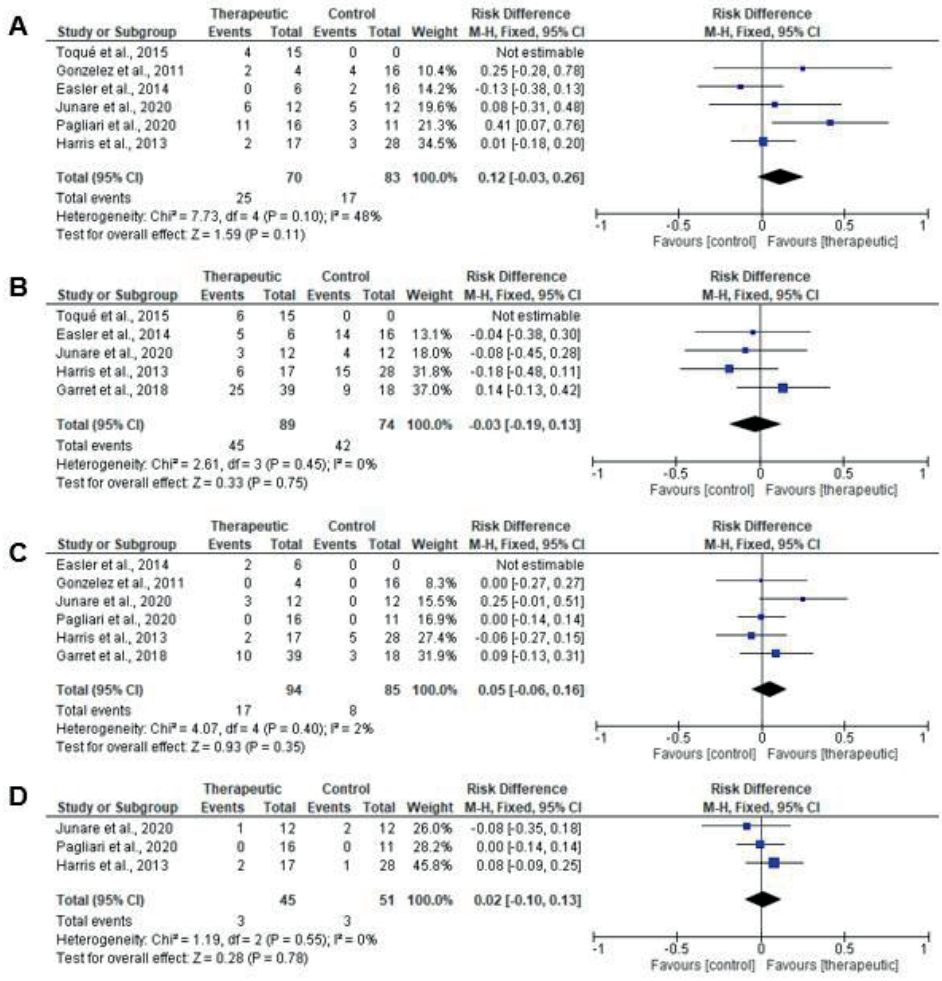
OR "cows" OR "bovine" OR "goat" OR "goats" OR "sheep" OR "ovine" OR "canine" OR "dog" OR "dogs" OR "feline" OR "cat" OR "cats")

Emcare

(((*"acute pancreatitis"/ OR "acute pancreatitis".ti,ab OR ((exp *"Pancreatitis"/ OR "pancreatitis".ti,ab) AND (*"Acute Disease"/ OR "acute*".ti,ab))) AND (exp *"Thrombosis"/ OR "Thrombosis".ti,ab OR "Thrombo*".ti,ab OR "Thrombus".ti,ab OR "Thrombi".ti,ab OR "blood clot*".ti,ab OR "Budd-Chiari*".ti,ab OR "Postthrombo*".ti,ab OR "Retinal Vein Occlu*".ti,ab OR "Thrombophleb*".ti,ab OR "Lemierre Syndrome".ti,ab OR "DVT".ti,ab OR "vascular complicat*".ti,ab OR exp *"Vascular Disease"/) AND (exp *"Anticoagulant Agent"/ OR "Anticoagula*".ti,ab OR "Anti coagula*".ti,ab OR "(2S)-2-(4-(((3S)-1-acetimidoyl-3-pyrrolidinyl)oxy)phenyl)-3-(7-amidino-2-naphtyl)propanoic acid".ti,ab OR "1-(1-(3-((6-chloronaphthalen-2-yl)sulfonyl)-2-hydroxypropanoyl)piperidin-4-yl) tetrahydropyrimidin-2(1H)-one".ti,ab OR "1-(1-amino-7-isoquinolyl)-N-(2'-(aminosulfonyl)-1,1'-biphenyl-4-yl)-3-methyl-1H-pyrazole-5-carboxamide".ti,ab OR "1-(2,2-difluoroethyl)pyrrolidine-3,4-dicarboxylic acid 3-((5-chloropyridin-2-yl)amide) 4-((2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl)amide)".ti,ab OR "1-(3-(aminomethyl)phenyl)-N-(3-fluoro-2'-(methylsulfonyl) (1,1'-biphenyl)-4-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide".ti,ab OR "1-(3-aminobenzisoxazol-5'-yl)-3-trifluoromethyl-6-(2'-(3-hydroxy-N-pyrrolidinyl) methyl-(1,1')-biphen-4-yl)-1,4,5,6-tetrahydropyrazolo-(3,4-c)-pyridin-7-one".ti,ab OR "2-(1-(3-((6-chloronaphthalen-2-yl)sulfonyl)propanoyl)piperidin-4-yl)-5-methyl-1,2-dihydro-3H-imidazo(1,5-c)imidazol-3-one".ti,ab OR "2-(4-(dimethylamino)benzoylamino)-5-methanesulfonylamino-N'-(4-methoxyphenyl) benzamide".ti,ab OR "2-(5-chlorothien-2-yl)-N-(1-(1-methyl-2-(morpholin-4-yl)-2-oxoethyl)-2-oxopyrrolidin-3-yl)ethenesulfonamide".ti,ab OR "2-carbamoyl-4-((6-chloronaphthalen-2-yl)sulfonyl)-1-((5-methyl-4,5,6,7-tetrahydrothiazolo(5,4-c) pyridin-2-yl)carbonyl)piperazine".ti,ab OR "3,3'-(3,5-difluoro-4-methyl-2,6-pyridinediylbis(oxy))bis(benzenecarbox(imide)amide)".ti,ab OR "3-(4-(5-(2,6-dimethylpiperidin-1-yl)pentyl)-3-oxo-3,4-dihydroxyquinoxalin-2-yl)benzamidine".ti,ab OR "3-(4-(5-(2,6-dimethyltetrahydro-1(2H)-pyridinyl)pentyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-2-yl)-1-benzenecarboximidamide".ti,ab OR "3-chloro-N-(4-chloro-2-(((5-chloro-2-pyridinyl)amino)carbonyl)-6-methoxyphenyl)-4-(((4,5-dihydro-2-oxazolyl)methylamino)methyl)-2-thiophenecarboxamide".ti,ab OR "3-chloro-N-(4-chloro-2-(((5-chloro-2-pyridinyl)amino)carbonyl)-6-methoxyphenyl)-4-((methylamino)methyl)-2-thiophenecarboxamide".ti,ab OR "4-((2-amidino-1,2,3,4-tetrahydroisoquinolin-7-yloxy)methyl)-1-(4-pyridinyl) piperidine-4-carboxylic acid monomethanesulfonate trihydrate".ti,ab OR "4-Hy-

droxycoumarins".ti,ab OR "5-chlorothiophene-2-carboxylic acid (2-(2-methyl-3-(2-oxopyrrolidin-1-yl)benzenesulfonylamino)-3-(4-methylpiperazin-1-yl)-3-oxopropyl)amide".ti,ab OR "6-(dimethylcarbamoyl)nicotinoyl guanidine".ti,ab OR "6-chloromethyl-3-(2,5-dichlorophenoxycarbonyl)-2-benzopyrone".ti,ab OR "6-methyl-1,2,3,5-tetrahydroimidazo(2,1-b)quinazolin-2-one hydrochloride".ti,ab OR "Abciximab".ti,ab OR "Acenocoumarol".ti,ab OR "acid citrate dextrose".ti,ab OR "alpha-(3-amidinylphenoxy)-2-bromo-N-(5-(pyrrolidin-1-ylcarbonyl)phenyl) phenylacetamide".ti,ab OR "Ancrod".ti,ab OR "antistasin".ti,ab OR "Antithrombin III".ti,ab OR "Antithrombin Proteins".ti,ab OR "antivitamins K".ti,ab OR "apixaban".ti,ab OR "aprosulate".ti,ab OR "ardeparin".ti,ab OR "argatroban".ti,ab OR "Becaplermin".ti,ab OR "bemiparin".ti,ab OR "beta 2-Glycoprotein I".ti,ab OR "betrixaban".ti,ab OR "bivalirudin".ti,ab OR "Blood Coagulation Factor Inhibitors". ti,ab OR "BMS 269223".ti,ab OR "BnSO(2)-D-Arg-Gly-Arg-ketothiazole".ti,ab OR "bromadiolone".ti,ab OR "bromfenacoum".ti,ab OR "calcium heparin".ti,ab OR "certoparin".ti,ab OR "chlorophacinone".ti,ab OR "citrate phosphate dextrose".ti,ab OR "Citric Acid".ti,ab OR "clocoumarol".ti,ab OR "coumachlor".ti,ab OR "CPDA solutions".ti,ab OR "Dabigatran".ti,ab OR "Dalteparin".ti,ab OR "danaparoid".ti,ab OR "darexaban".ti,ab OR "Dermatan Sulfate".ti,ab OR "desirudin".ti,ab OR "Dextrans". ti,ab OR "Dicumarol".ti,ab OR "difenacoum".ti,ab OR "DPC 602".ti,ab OR "Edetic Acid".ti,ab OR "efegatran".ti,ab OR "eisenstasin".ti,ab OR "Enoxaparin".ti,ab OR "Ethyl Biscoumacetate".ti,ab OR "factor Xa, Glu-Gly-Arg-".ti,ab OR "ferulic acid". ti,ab OR "Fibrin Fibrinogen Degradation Products".ti,ab OR "fibrinogen fragment X".ti,ab OR "fluindione".ti,ab OR "Fondaparinux".ti,ab OR "fucoidan".ti,ab OR "FX 2212".ti,ab OR "Gabexate".ti,ab OR "glucuronyl glucosamine glycan sulfate". ti,ab OR "Heparin".ti,ab OR "Heparin Cofactor II".ti,ab OR "Heparin, Low-Molecular-Weight".ti,ab OR "Heparinoids".ti,ab OR "Hirudins".ti,ab OR "HY023016". ti,ab OR "idrabiotaparinux".ti,ab OR "idraparinux".ti,ab OR "inogatran".ti,ab OR "isoleucyl-glutamyl-glycyl-arginine chloromethyl ketone".ti,ab OR "ITF 1331".ti,ab OR "lamifiban".ti,ab OR "laminaran".ti,ab OR "lefaxin".ti,ab OR "lepirudin".ti,ab OR "lipoprotein-associated coagulation inhibitor".ti,ab OR "lufaxin protein, Lutzomyia longipalpis".ti,ab OR "melagatran".ti,ab OR "moxicoumone".ti,ab OR "N(2)-(4-(dimethylamino)benzoyl)-4-hydroxy-N(1)-(4-methoxybenzoyl)-1,2-benzenediamine".ti,ab OR "N(alpha)-(2-naphthylsulfonylglycyl)-4-amidinophenylalanine piperidide".ti,ab OR "N-(4-(1-(acetimidoyl)piperidin-4-yloxy)-3-carbamoylphenyl)-N-(3-(3-amidinophenyl)-2-fluoro-2-propenyl)sulfamoylacetic acid".ti,ab OR "N-(4-chlorophenyl)-N-(2-fluoro-4-(2-oxopyridin-1(2H)-yl)phenyl)-4-methoxypyrrolidiine-1,2-dicarboxamide".ti,ab OR "Nadroparin".ti,ab OR "nafamostat". ti,ab OR "nitrophorin".ti,ab OR "otamixaban".ti,ab OR "parnaparin".ti,ab OR "PD0313052".ti,ab OR "PENTA".ti,ab OR "Pentosan Sulfuric Polyester".ti,ab OR "Phenindione".ti,ab OR "Phenprocoumon".ti,ab OR "plumbagin".ti,ab OR "Protein

C".ti,ab OR "Protein S".ti,ab OR "protocatechualdehyde".ti,ab OR "pyragrel".ti,ab OR "reviparin".ti,ab OR "Rivaroxaban".ti,ab OR "RPR 120844".ti,ab OR "RPR 130737".ti,ab OR "RPR 208566".ti,ab OR "RPR 209685".ti,ab OR "RWJ 445167". ti,ab OR "SDZ MTH 958".ti,ab OR "SE 170".ti,ab OR "SEL 2711".ti,ab OR "SF 324".ti,ab OR "Sodium Citrate".ti,ab OR "SV-66 protein, Simulium vittatum".ti,ab OR "tanshinone".ti,ab OR "therostasin protein, Theromyzon tessulatum".ti,ab OR "tick anticoagulant peptide".ti,ab OR "Tinzaparin".ti,ab OR "tocopherylquinone". ti,ab OR "troxerutin".ti,ab OR "Warfarin".ti,ab OR "WX-FX4 compound".ti,ab OR "ximelagatran".ti,ab OR "YM 60828".ti,ab OR "ZK 805412".ti,ab OR "ZK 806299". ti,ab)) OR ((*"acute pancreatitis"/ OR "acute pancreatitis".ti OR ((exp *"Pancreatitis"/ OR "pancreatitis".ti) AND (*"Acute Disease"/ OR "acute*".ti))) AND (exp *"Thrombosis"/ OR "Thrombosis".ti,ab OR "Thrombo*".ti,ab OR "Thrombus".ti,ab OR "Thrombi".ti,ab OR "blood clot*".ti,ab OR "Budd-Chiari*".ti,ab OR "Postthrombo*".ti,ab OR "Retinal Vein Occlu*".ti,ab OR "Thrombophleb*".ti,ab OR "Lemierre Syndrome".ti,ab OR "DVT".ti,ab OR "vascular complicat*".ti,ab))) NOT (exp "Animals"/ NOT exp "Humans"/) AND english.la



Supplementary figure S1. Meta-analysis for recanalization (A), varices, collaterals or cavernoma (B), hemorrhage (C), and mortality (D) with a fixed-effects model

CHAPTER 4

Therapeutic anticoagulation for splanchnic vein thrombosis in acute pancreatitis: *a national survey and case-vignette study*

World Journal of Gastroenterology 2023

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ABSTRACT

Introduction: Splanchnic vein thrombosis (SVT) is a major complication of moderate and severe acute pancreatitis. There is no consensus on whether therapeutic anticoagulation should be started in patients with acute pancreatitis and SVT.

Aim: To gain insight into current opinions and clinical decision making of pancreatologists regarding SVT in acute pancreatitis.

Methods: A total of 139 pancreatologists of the Dutch Pancreatitis Study Group and Dutch Pancreatic Cancer Group were approached to complete an online survey and case vignette survey. The threshold to assume group agreement was set at 75%.

Results: The response rate was 67% (n=93). Seventy-one pancreatologists (77%) regularly prescribed therapeutic anticoagulation in case of SVT, and 12 pancreatologists (13%) for narrowing of splanchnic vein lumen. The most common reason to treat SVT was to avoid complications (87%). Acute thrombosis was the most important factor to prescribe therapeutic anticoagulation (90%). Portal vein thrombosis was chosen as the most preferred location to initiate therapeutic anticoagulation (76%) and splenic vein thrombosis as the least preferred location (86%). The preferred initial agent was low molecular weight heparin (LMWH; 87%). In the case vignettes, therapeutic anticoagulation was prescribed for acute portal vein thrombosis, with or without suspected infected necrosis (82% and 90%), and thrombus progression (88%). Agreement was lacking regarding the selection and duration of long-term anticoagulation, the indication for thrombophilia testing and upper endoscopy, and about whether risk of bleeding is a major barrier for therapeutic anticoagulation.

Conclusion: In this national survey, the pancreatologists seemed to agree on the use of therapeutic anticoagulation, using LMWH in the acute phase, for acute portal thrombosis and in the case of thrombus progression, irrespective of the presence of infected necrosis.

INTRODUCTION

Acute pancreatitis is an inflammatory disorder of the pancreas and is self-limiting in the majority of patients (1, 2). However, approximately 20% of patients develop a moderate or severe disease course, with (peri)pancreatic necrosis and collections (3, 4). Due to the combination of local inflammation and mechanical compression, these complications may cause thrombus formation in the splanchnic circulation, including the portal, splenic and superior mesenteric vein (5, 6). The reported estimates on the incidence of splanchnic vein thrombosis (SVT) in acute pancreatitis range from 17 to 23%, and are even higher in complicated acute pancreatitis (7, 8). The clinical presentation of SVT varies between an asymptomatic thrombus to potential lethal complications, such as portal or left side hypertensive bleeding and small bowel ischemia (9-11). For this reason, early treatment with therapeutic anticoagulation is recommended in patients with acute SVT (12-14). However, consistent evidence to drive this decision in acute pancreatitis patients does not exist (15-18). In fact, a recent meta-analysis from our study group showed that 53% of acute pancreatitis patients do not receive therapeutic anticoagulation (15). This proportion of untreated patients is substantially higher than previously reported in other SVT populations (19), probably because of the fear of serious bleeding. Variation in clinical practice also became apparent in this meta-analysis (15), as anticoagulation use and the type of agent used were very heterogeneous between studies. Therefore, the aim of this survey was to gain more insight into current opinions of pancreatologists on anticoagulation therapy for SVT following acute pancreatitis.

METHODS

We conducted an online national survey and case vignette study among members of the Dutch Pancreatitis Study Group (DPSG) and the Dutch Pancreatic Cancer Group (DPCG). Members were excluded if they were not primary care-takers in the treatment of patients with AP (e.g. radiologists, oncologists, basic scientists). The survey was built in Research Electronic Data Capture, and invitations to participate were sent by e-mail in November 2021, followed by four weekly reminders. Additionally, the survey was promoted through newsletters and during annual study group meetings of the DPSG and DPCG.

Survey design

The survey was developed by a multidisciplinary team of surgeons, gastroenterologists, and radiologists, and included 3 demographical questions, 17 general questions and 3 case vignettes (supplementary material). Demographic information included the

responders' specialty, type of hospital and working experience. The general questions focused on treatment of SVT and potential factors that may influence the responders' decision. The case-vignettes addressed the preferred treatment strategy in different clinical cases at different time points. All cases however, concerned a 50-year old male patient with acute alcoholic necrotising pancreatitis, and can be summarized as follows:

Case vignette 1: A patient visited the emergency department, 5 d after onset of abdominal pain. Contrast-enhanced CT (CECT) showed necrotising pancreatitis with acute necrotic collection in the head of the pancreas (figure 1A) and:

A1: Luminal narrowing of the portal vein without the presence of collateral circulation (figure 1B)

A2: Intraluminal filling defect in the portal vein without the presence of collateral circulation

A3: Intraluminal filling defect in the portal vein without the presence of collateral circulation + a pseudoaneurysm in the proximal splenic artery (figure 1C)

Case vignette 2: A patient admitted to the ward, 14 d after onset of abdominal pain. The patient showed signs of clinical detoriation with fever and rising inflammatory parameters. The CECT showed almost fully encapsulated pancreatic necrosis without gas configurations (figure 1D) and a new intraluminal filling defect in the portal vein without the presence of collateral circulation (figure 1E). The diagnosis of suspected infected pancreatic necrosis was made.

Case vignette 3: A homeless patient visited the emergency department, 30 d after onset of vague abdominal pain. CECT showed necrotising pancreatitis and:

CA: Intraluminal filling defect in the portal vein with the presence of collateral circulation

CB: Thrombus progression and expansion of the collateral circulation (figure 1F)

The threshold to assume group agreement was set at 75%. If a question ranged from always, usually, sometimes and never, agreement was defined when 75% of the pancreatologists rated it as always or usually (*regularly)*, or sometimes and never (*infrequently)*.

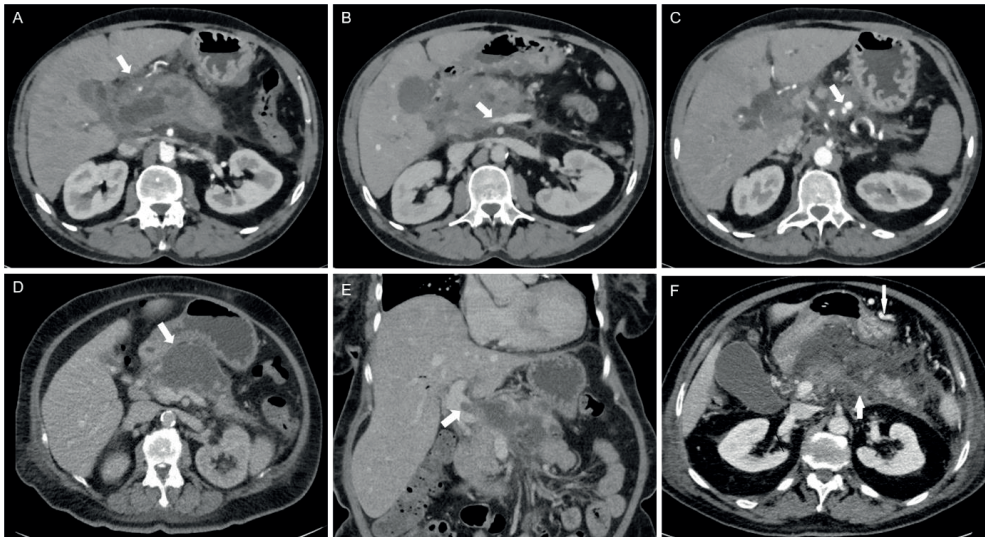

Figure 1. Imaging findings of case vignette

A: acute necrotic collection in the head of the pancreas in vase vignette 1; B: Luminal narrowing of the portal vein without the presence of collateral circulation in case vignette 1; C: Pseudoaneurysm in the proximal splenic artery in case vignette 1; D: Almost fully encapsulated pancreatic necrosis without gas configurations in case vignette 2; Luminal filling defect in the portal vein without the presence of collateral circulation in case vignette 2; F: Extension of the thrombus to the splenic vein (arrow pointing upwards) and expansion of the collateral pathway in the gastroepiploic veins along the great curvature of the stomach (arrow pointing downwards) in case vignette 3.

Definitions

SVT was predefined as an actual intraluminal filling defect on imaging of one or more of the splanchnic veins. The chronicity was divided into (sub)acute thrombosis or chronic thrombosis (with concomitant collaterals), anatomical location into portal, splenic and/or superior mesenteric vein, degree into a total or partial occlusion and extent into an isolated thrombus or a thrombus in several venous segments. Thrombus progression was defined as progression into other splanchnic vein(s), into total occlusion, or both.

Statistical analysis

Descriptive data are presented as counts with proportions for categorical data. All analyses were performed using IBM SPSS (20).

RESULTS

A total of 93 of the 139 invited pancreatologists (67%) responded and participated in this survey and case vignette study; 67 gastroenterologists (72%), 25 surgeons (27%) and 1 intensivist (1%). The majority worked in a non-academic centre (70%) and had more than 10 years of experience in treating AP patients (60%). Demographic characteristics are presented in Table 1.

Table 1. Details of respondents

Demographics	***n* = 93 (%)**
Specialty	
Surgeon	25 (27%)
Gastroenterologist	67 (72%)
Intensivist	1 (1%)
Type of hospital	
Academic	28 (30%)
Non-academic, teaching hospital	60 (65%)
Non-academic, non-teaching hospital	5 (5%)
Experience in treating patients with acute pancreatitis	
0-5 years	10 (11%)
5-10 years	27 (29%)
10-15 years	17 (18%)
15-20 years	23 (25%)
> 20 years	16 (17%)

Indications for and details of treatment with therapeutic anticoagulation

Agreement was reached on whether therapeutic anticoagulation should be prescribed for SVT and luminal narrowing of one or more of the splanchnic veins in acute pancreatitis patients. For SVT, therapeutic anticoagulation was regularly prescribed by 71 (76%) and infrequently by 22 (24%) pancreatologists. In case of luminal narrowing, therapeutic anticoagulation was only regularly prescribed by 12 (13%) pancreatologists. Avoiding complications, such as portal hypertension and bowel ischemia, was the main reason for 81 pancreatologists (87%) to start therapeutic anticoagulation. Screening for an underlying prothrombotic disorder in patients diagnosed with SVT was regularly performed by 14 (15%) pancreatologists, only in patients with a history of one (or more) thrombotic events by 40 (43%), and infrequently by 39 (42%) pancreatologists. There was agreement on the preferred initial type of therapeutic anticoagulation for SVT (81 pancreatologists (87%) preferred subcutaneous low-molecular-weight heparin (LMWH)), but not on the preferred follow-up type. Imaging after the index admission was chosen as follow-up strategy by 79 pancreatologists (85%). Thirteen pancreatologists (13%) indicated that they usually stop anticoagulant

therapy in case of achieved radiological recanalization, 35 (38%) after a period of 3 mo, 42 (45%) after 6 mo, and 3 (3%) after 12 mo. All details are provided in Table 2.

Table 2. Survey results: indication for and details of treatment with therapeutic AC

	Total (*n* = 93)
Do you prescribe therapeutic AC in case of detected thrombosis in one (or more) of the splanchnic veins?	
Always	23 (25%)
Usually	48 (52%)
Sometimes	21 (23%)
Never	1 (1%)
Do you prescribe therapeutic AC in case of detected luminal narrowing of one (or more) of the splanchnic veins?	
Always	3 (3%)
Usually	9 (10%)
Sometimes	29 (31%)
Never	52 (56%)
Main reason(s) to start therapeutic AC *(multiple answers were possible)*	
To achieve vessel recanalization	52 (56%)
To avoid complications	81 (87%)
To prevent formation of altered venous anatomy	31 (33%)
To prevent recurrence of SVT	27 (29%)
To prevent other venous thromboembolism	30 (32%)
Other reason*	1 (1%)
Do you screen for an underlying prothrombotic disorder?	
Always	2 (2%)
Usually	12 (13%)
Sometimes	25 (27%)
Only in patients with a history of one (or more) thrombotic events	40 (43%)
Never	14 (15%)
Which initial type of therapeutic AC do you prefer?	
(Low molecular weight) heparin subcutaneous	81 (87%)
Unfractionated heparin intravenous	4 (4%)
Direct oral anticoagulation	3 (3%)
Vitamin K antagonist	4 (4%)
Platelet aggregation inhibitor	1 (1%)
Urokinase/ recombinant tissue plasminogen activator	0

Table 2. Survey results: indication for and details of treatment with therapeutic AC (*continued*)

Which follow-up type of therapeutic AC do you prefer?	
(Low molecular weight) heparin subcutaneous	9 (10%)
Unfractionated heparin intravenous	0
Direct oral anticoagulation	53 (57%)
Vitamin K antagonist	29 (31%)
Platelet aggregation inhibitor	2 (2%)
Urokinase/ recombinant tissue plasminogen activator	0
Do you generally follow-up SVT after index admission?	
Yes, clinically only	5 (5%)
Yes, with imaging	79 (85%)
No	9 (10%)
After how long do you usually stop the therapeutic AC?	
In case of achieved radiological recanalization	13 (14%)
3 months	35 (38%)
6 months	42 (45%)
12 months	3 (3%)
Never	0

**In free text: expansion of thrombosis. Abbreviations: AC anticoagulation, SVT splanchnic vein thrombosis.*

Determinants of prescribing therapeutic anticoagulation

Seventy-eight pancreatologists (84%) have chosen the time course of thrombosis as the most important factor supporting anticoagulant therapy; 84 pancreatologists (90%) prescribe therapeutic anticoagulation in case of a (sub)acute thrombosis *vs* 9 (10%) for both (sub)acute and chronic thrombosis. Moreover, 70 pancreatologists (76%) have chosen portal vein thrombosis as the most preferred location to initiate therapeutic anticoagulation, whereas splenic vein thrombosis was chosen as least preferred location by 80 pancreatologists (86%). The majority of pancreatologists (85%) treat both total and partial occlusive thrombosis. There was no agreement whether the risk of different types of bleeding should be considered as a major barrier to prescribe therapeutic anticoagulation. The need for invasive interventions for local complications of acute pancreatitis influenced the decision whether or not to initiate anticoagulation therapy in about half of pancreatologists (52%). All details are outlined in Table 3.

Statements on prognosis

An association between the presence of SVT and worse clinical outcomes in patients with acute pancreatitis was assumed by 67 pancreatologists (72%) (Figure 2). Moreover, the vast majority (88%) agreed that therapeutic anticoagulation for splanchnic vein thrombosis improves clinical outcomes in these patients. Insufficient evidence was the most frequently quoted reason among pancreatologists who disagreed with this second statement.

Table 3. Survey results: determinants of prescribing therapeutic AC

	Total (*n* = 93)
Do you consider … of the thrombosis as an important factor to prescribe therapeutic AC? *(multiple answers were possible)*	
Age (acute or chronic)	78 (84%)
Anatomical location (portal, splenic or superior mesenteric vein)	42 (45%)
Degree (total or partial)	45 (48%)
Extent (isolated thrombosis or thrombosis in several segments)	49 (53%)
Progression (over time)	40 (43%)
When do you prescribe therapeutic AC? In case of:	
(Sub)acute thrombosis	84 (90%)
Chronic thrombosis	0
Both	9 (10%)
Rank the anatomical location of the thrombosis from most likely to less likely to start therapeutic AC:	
Portal vein – splenic vein – superior mesenteric vein	9 (10%)
Portal vein – superior mesenteric vein – splenic vein	61 (66%)
Splenic vein – portal vein – superior mesenteric vein	0
Splenic vein – superior mesenteric vein – portal vein	1 (1%)
Superior mesenteric vein – portal vein – splenic vein	19 (20%)
Superior mesenteric vein – splenic vein – portal vein	3 (3%)
When do you prescribe therapeutic AC? In case of:	
Total thrombosis	9 (10%)
Partial thrombosis	5 (5%)
Both	79 (85%)
Do you consider the risk of ... as a major barrier to prescribe therapeutic AC? *(multiple answers were possible)*	
Bleeding in general	52 (56%)
Bleeding related to portal hypertension	17 (18%)
Bleeding related to pseudoaneurysm	49 (53%)
Other risk	1 (1%)
Does the need for invasive interventions for local complications of acute pancreatitis influence your decision regarding AC therapy?	
Yes	48 (52%)
No	45 (48%)

**In free text: CVA bleeding history. Abbreviations: AC anticoagulation, SVT splanchnic vein thrombosis.*

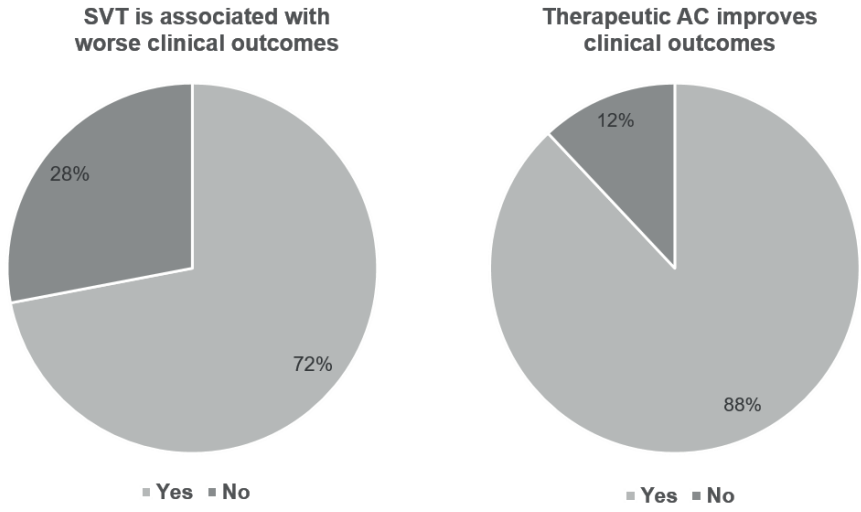

Figure 2. Statements on prognosis
Abbreviations: AC anticoagulation, SVT splanchnic vein thrombosis.

Case-vignettes

The results of the case vignettes are summarized in Figure 3. In the first case vignette (patient 1, day 5 of acute necrotising pancreatitis), 11 pancreatologists (12%) would prescribe a therapeutic dose anticoagulation if luminal narrowing without collateral circulation was detected in the portal vein. Of the 82 pancreatologists (88%) who opted for no therapeutic dose anticoagulation, 73 (89%) would change treatment strategy in case an actual filling defect in the portal vein was detected. In total, 84 pancreatologists (90%) would prescribe therapeutic dose anticoagulation to this patient with an actual portal vein thrombosis without collateral circulation. If a pseudoaneurysm was concomitantly present, 43 of those 84 pancreatologists (51%) who favoured a therapeutic dose anticoagulation would switch to a prophylactic dose anticoagulation (n=28, 65%) or no anticoagulation at all (n=15, 35%), leaving 41 pancreatologists (44%) in the therapeutic anticoagulation group.

In the second case vignette (patient 2, day 14 of suspected infected necrotising pancreatitis), 77 pancreatologists (82%) would prescribe therapeutic dose anticoagulation if a portal vein thrombosis without collateral circulation was detected. The presence of (suspected) infected pancreatic necrosis influenced the choice of anticoagulation agent in 49 pancreatologists (52%). Almost all of these pancreatologists pointed out that once infected pancreatic necrosis is suspected, they would choose an agent with a short half-life because of the potentially need of invasive intervention.

In the third case vignette (patient 3, day 30 of acute necrotising pancreatitis), 44 pancreatologists (47%) would prescribe a therapeutic dose anticoagulation if a portal vein thrombosis with collateral circulation was detected. Of these 44 pancreatologists, 19 (43%) would perform upper endoscopy to screen for and- if present-treat oesophageal varices before starting anticoagulation therapy. In case of thrombus progression (extension of the thrombus to the splenic vein and expansion of the collateral pathway), 11 pancreatologists (12%) would stay conservative (i.e., no therapeutic dose of anticoagulation), 82 (88%) would start or continue a therapeutic dose anticoagulation and none would proceed to an intervention.

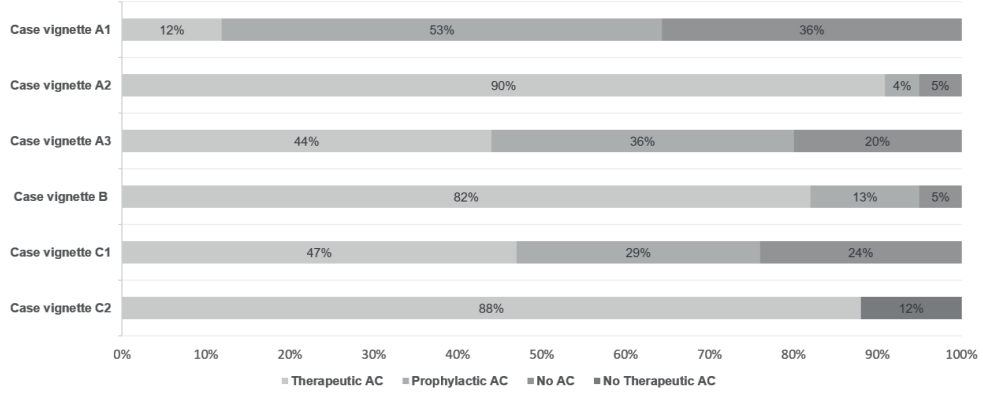

Figure 3. Case vignette results: choice of treatment
Abbreviations: AC anticoagulation.

DISCUSSION

This first nationwide survey and case vignette study gives insight into the clinical scenarios in which therapeutic anticoagulation is currently used, and not used to treat or prevent splanchnic vein thrombosis in acute pancreatitis patients. In an earlier study (15), we found 7 retrospective cohort studies evaluating therapeutic anticoagulation in this patient category with conflicting results in clinical outcome (21-27). These studies were of moderate quality and therefore the pancreatologist' preference and belief predominate in current decision making rather than scientific evidence.

An important finding of the current study was that more than 75% of pancreatologists regularly prescribe therapeutic anticoagulation for SVT, particularly for a thrombus that acutely developed. This is in line with recommendations from general guidelines for SVT management (12-14). In the absence of a visualized thrombus, most pancreatologists indicated not to treat compressed veins with anticoagulation.

Although wall shear stress in a compressed vessel may promote platelet activation, and subsequently thrombus formation (28), there is no data yet to question the opinion of the pancreatologists.

In this study, the most important reason to administer therapeutic anticoagulation was to avoid complications including bowel ischemia and portal hypertension. Bowel ischemia has been reported in up to 33% of acute pancreatitis patients treated with therapeutic anticoagulation *vs* 16% of untreated patients (22, 24, 25). A potential explanation for this discrepancy could be that bowel ischemia was already present prior to the start of therapy, therefore being an indication for therapeutic anticoagulation rather than a consequence. In addition, the presence of varices and other collaterals have been equally reported (15), and only one of the aforementioned studies described one case of bleeding from oesophageal varices in an anticoagulated patient (24). Again, it is likely that a perceived bleeding risk influenced the decision whether or not to prescribe therapeutic anticoagulation. This confounding by indication clearly limits the interpretation of these retrospective studies.

Achieving vessel recanalization was chosen as the second goal. A recent meta-analysis showed that the pooled rate of recanalization of SVT was similar between treated (36%) and untreated patients (31%) (15). However, there is reason to believe that the benefit of anticoagulation therapy may alter when considering the anatomical location of the thrombosis (21, 29). Patients with portal vein or superior mesenteric vein thrombosis may have an increased risk of complications, while having lower spontaneous recanalization rates. In particular, mortality rates of patients with superior mesenteric vein thrombosis are reported up to 50% (30, 31). On the other hand, splenic vein thrombosis, which is by far the most common site of thrombosis in acute pancreatitis patients, forms a less serious concern for gastrointestinal bleeding and insufficient recanalization (8, 26, 32). A selective anticoagulation policy, in which therapeutic anticoagulation was reserved for portal- and superior mesenteric vein thrombosis, was recently assessed in a retrospective study (33). This study showed a recanalization rate of 67% in portal- and superior mesenteric vein thrombosis, which is substantially higher than previously reported (15). In addition, a recent practice guideline from the Pancreas study group, Chinese Society of Gastroenterology, recommends a selective anticoagulation policy (34). In this survey, portal vein thrombosis, followed by superior mesenteric vein thrombosis, was also the pancreatologists' preferred location for prescribing therapeutic anticoagulation, while splenic vein was the least preferred location.

With respect to chronic SVT, the current guidelines do not recommend therapeutic anticoagulation (10). This is in line with the reported use in case vignette 3, with

the exception of the case of the patient with thrombus progression and expansion of the collateral circulation. In this scenario, 88% of pancreatologists would treat such patient with therapeutic anticoagulation. A recent multicentre randomised controlled trial comparing daily rivaroxaban 15mg/d to no anticoagulation in patients with noncirrhotic chronic portal vein thrombosis (35), formally challenged the guideline recommendations. This study showed that rivaroxaban, even in prophylactic dose, reduced the incidence of venous thromboembolism; therefore, this study may initiate a shift towards a more frequent use of anticoagulation in chronic SVT. On that note, primary prophylaxis of portal hypertensive bleeding should be performed, as laid out by the BAVENO IV guideline(36). In this survey, however, the minority of pancreatologists followed this recommendation. Improvements should also be made to distinguish acute from chronic SVT. Currently, no clear definition for chronic SVT exists other than a presumed time course of more than 6 mo or the presence of multiple small collaterals around the obstructed veins (10, 13), which is not useful to diagnose a nonocclusive chronic thrombosis (i.e. absence of collateral pathways). A promising invention to overcome this problem is magnetic resonance noncontrast thrombus imaging, though validation is still needed (37).

According to our survey, subcutaneous LMWH was the favoured initial type of therapeutic anticoagulation, while no agreement regarding the choice of long-term anticoagulation and its duration was found. In current guidelines, switching LMWH to a vitamin K antagonist once reaching the target range is the reported strategy for patients with SVT (12-14, 38). The use of direct oral anticoagulation (i.e., apixaban) in acute pancreatitis patients with SVT is reported in two studies and showed comparable results (21, 33). However, in the case of (suspected) infected pancreatic necrosis, LMWH seems to be preferred by more than half of the pancreatologists, due to its short half-life and reversibility. Besides, many acute pancreatitis patients have reduced caloric intake limiting the absorption of DOACS. Therefore, it seems fair to advise LWMH, especially in the acute phase. Looking at the duration of anticoagulation therapy for provoked SVT in patients with a transient risk factor, such as acute pancreatitis, the suggested duration is 3 to 6 mo (12-14, 38). Consistently, 38% and 45% of the pancreatologists in our survey preferred 3 and 6 mo treatment duration, respectively.

Based on the available literature, it remains unclear whether therapeutic anticoagulation is associated with higher rates of bleeding. An increased bleeding risk with therapeutic anticoagulation has been reported up to 33% of patients (21, 25, 26), but there are also studies showing lower rates of bleeding (24). The theory for this latter finding is that therapeutic anticoagulation prevents thrombus progression, therefore reducing the portal pressure and consequently the risk of bleeding (19). In this study,

the risk of bleeding was not identified as a significant discouraging factor, as only about half of the pancreatologists considered bleeding in general and bleeding related to pseudoaneurysm as a major barrier to prescribe therapeutic anticoagulation. Also, the possible need for invasive intervention, due to suspected infected necrosis, did not significantly influence the treatment strategy. Another critical question is whether SVT influences the disease course of acute pancreatitis patients, but again this remains unanswered (15). In this survey, the majority of pancreatologists assumed that the occurrence of SVT is associated with worse clinical outcomes, and interestingly, even more pancreatologists were convinced that the use of therapeutic anticoagulation leads to improved patient outcomes.

A strength of this study is the response rate of 67%, which is relatively high compared to previous surveys among pancreatologists (39-41). Furthermore, the ratio of 30:70 between academic and non-academic pancreatologists attributed to a valuable insight into the pancreatologists' opinions on the use of therapeutic anticoagulation. This study also has several limitations. First, the results may not directly reflect the actual practice in other countries as only members of two Dutch associations of pancreatology were invited. This decision was made to avoid selection based on publication record, and consequently include pancreatologists who are not actively involved in the treatment of acute pancreatitis (40). Another advantage of our method is that it allowed us to calculate the survey's response rate by bypassing the confidentiality of membership lists of international pancreatic associations. Second, the clinical presentation of SVT is very heterogeneous, as well as the patient characteristics and clinical disease course among acute pancreatitis patients, which influences current decision making. For this reason, it might have been difficult for pancreatologists to answer some of the general questions. Therefore, case vignettes were used to explore what considerations underpin their decisions. As the descriptions throughout the case vignettes were consistently formulated and only one clinical detail was changed at a time, treatment of patients with superior mesenteric vein and splenic vein thrombosis was not assessed in the case vignettes. Consequently, the pancreatologists' preference on this manifestation of SVT in acute pancreatitis remained unknown. Finally, the rationale behind the "nonprescribing trend" was not assessed adequately, which could be a focus for future research.

CONCLUSION

This national survey demonstrates the tendency of pancreatologists to prescribe therapeutic anticoagulation for acute thrombosis, in particular for acute portal vein thrombosis and in case of thrombus progression, irrespective of the presence of in-

fected necrosis. With therapeutic anticoagulation, the majority of pancreatologists believed that the clinical outcomes of acute pancreatitis patients with splanchnic vein thrombosis will improve. Furthermore, this study reflects on several knowledge gaps in literature, and sets out clear points for future research. Specifically, a deeper understanding of the pathophysiology and natural course of splanchnic vein thrombosis secondary to acute pancreatitis would allow us to clarify the therapeutic role of anticoagulation.

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Supplementary file S1. Survey

Expert profile

1. What is your specialty?
- Surgeon
- Gastroenterologist
- Radiologist
- Other

1a. If other, what is your specialty:

2. In what kind of institution do you work?
- Academic hospital
- Non-academic, teaching hospital
- Non-academic, non-teaching hospital

3. How many years of experience do you have in treating patients with acute pancreatitis?
- 0-5 years
- 5-10 years
- 10-15 years
- 15-20 years
- >20 years

Clinical questions

1. Do you prescribe therapeutic anticoagulation in case of detected thrombosis in one (or more) of the splanchnic veins (portal vein, splenic vein and superior mesenteric vein) in patients with acute pancreatitis?
- Always
- Usually
- Sometimes
- Never

2. Do you prescribe therapeutic anticoagulation in case of detected luminal narrowing of one (or more) of the splanchnic veins in patients with acute pancreatitis?
- Always
- Usually
- Sometimes
- Never

3. What would be your main reason(s) to start therapeutic anticoagulation? (check all that apply)
- To achieve vessel recanalization
- To avoid complications (i.e. portal hypertension, bowel ischemia, hepatic failure)
- To prevent formation of altered venous anatomy (i.e. cavernoma/collaterals/varices)
- To prevent recurrence of splanchnic vein thrombosis
- To prevent other venous thromboembolism
- Other reason

3a. If other reason, what are other reasons to start therapeutic anticoagulation?

4. In my decision on anticoagulant therapy for splanchnic vein thrombosis, I consider ……. of the thrombosis as an important factor (check all that apply):
- Age
- Anatomical location
- Extent
- Progression
- Other factor

4a. If other factor, what are other important factors in your decision on anticoagulant therapy?

5. When do you prescribe therapeutic anticoagulation? In case of…:
- (Sub)acute thrombosis
- Chronic thrombosis
- Both

6. Rank the anatomical location of the thrombosis from most likely to less likely to start anticoagulant therapy:
- Portal vein – splenic vein – superior mesenteric vein
- Portal vein – superior mesenteric vein – splenic vein
- Splenic vein – portal vein – superior mesenteric vein
- Splenic vein – superior mesenteric vein – portal vein
- Superior mesenteric vein – portal vein – splenic vein
- Superior mesenteric vein – splenic vein – portal vein

7. When do you prescribe therapeutic anticoagulation? In case of…:
- Total thrombotic occlusion

- Partial thrombosis
- Both

8. Does the involvement of multiple vessels influence your decision regarding anticoagulant therapy?
- Yes
- No

9. In my decision on anticoagulant therapy for splanchnic vein thrombosis, I consider the risk of ……. as a major barrier (check all that apply):
- Bleeding in general
- Bleeding related to portal hypertension
- Bleeding related to pseudoaneurysm
- Other risk

9a. If other risk, what would be another barrier to prescribe therapeutic anticoagulation?

10. Does the need for invasive interventions for local complications of acute pancreatitis influence your decision regarding anticoagulant therapy for splanchnic vein thrombosis?
- Yes
- No

11. Which initial type of therapeutic anticoagulation do you prefer?
- (Low molecular weight) heparin s.c.
- Unfractionated heparin i.v.
- Direct oral anticoagulation (DOAC)
- Vitamin K antagonist
- Platelet aggregation inhibitor
- Urokinase / recombinant tissue plasminogen activator

12. And which follow-up type of therapeutic anticoagulation do you prefer?
- (Low molecular weight) heparin s.c.
- Unfractionated heparin i.v.
- Direct oral anticoagulation (DOAC)
- Vitamin K antagonist
- Platelet aggregation inhibitor
- Urokinase / recombinant tissue plasminogen activator

13. After how long do you usually stop the therapeutic anticoagulation?
- In case of achieved radiological recanalization
- 3 months
- 6 months
- 12 months
- Never

14. Do you generally follow-up splanchnic vein thrombosis after index admission?
- Yes, clinically only
- Yes, with imaging
- No

15. Do you screen for an underlying prothrombotic disorder in patients diagnosed with splanchnic vein thrombosis?
- Always
- Usually
- Only in patients with a history of one (or more) thrombotic events
- Never

16. Is in your opinion, splanchnic vein thrombosis associated with worse clinical outcomes (e.g. mortality, organ failure, bleeding and other complications) in patients with acute pancreatitis?
- Yes
- No

17. Do you think that therapeutic anticoagulation for splanchnic vein thrombosis improves clinical outcomes in patients with acute pancreatitis?
- Yes
- No

17a. Please explain

Case vignettes

Patient A:

The patient is a 50 year old, previously healthy man, presented to the emergency department with acute alcoholic pancreatitis
- 5 days after onset of abdominal pain

- Contrast-enhanced CT (CECT) shows necrotizing pancreatitis with acute necrotic collection in the head of the pancreas (figure 1A) and luminal narrowing of the portal vein without the presence of collateral circulation (figure 1B)

1. Would you treat this patient with anticoagulation?
- Yes, with therapeutic dose anticoagulation
- Yes, with prophylactic dose anticoagulation
- No

2. Would your treatment strategy be different when an actual filling defect is visualized in the portal vein?
- Yes
- No

2a. Please explain
An experienced radiologist reassessed the CECT and found a luminal filling defect in the portal vein. The radiologist also detected a pseudoaneurysm in the proximal splenic artery (figure 1C).

3. Would you treat this patient with anticoagulation?
- Yes, with therapeutic dose anticoagulation
- Yes, with prophylactic dose anticoagulation
- No

Patient B:
The patient is a 50 year old, previously healthy man, admitted to the ward with acute necrotizing pancreatitis
- 14 days after onset of acute pancreatitis
- Clinical deterioration with fever and rising inflammatory parameters
- CECT (compared to a CECT from 10 days ago) shows almost fully encapsulated pancreatic necrosis without gas configurations (figure 1D) and a new luminal filling defect in the portal vein without the presence of collateral circulation (figure 1E)
- The diagnosis of suspected infected pancreatic necrosis (as no other infection focus is found) and portal vein thrombosis are made
- You decide to treat with broad spectrum antibiotics and postpone drainage

1. Would you treat this patient with anticoagulation?
- Yes, with therapeutic dose anticoagulation
- Yes, with prophylactic dose anticoagulation

- No

2. Does the presence of (suspected) infected pancreatic necrosis influence your choice of anticoagulant agent?
- Yes
- No

2a. If yes, please explain
Patient C:
The patient is a 50 year old, homeless man, now presenting to the emergency department with acute alcoholic pancreatitis
- 30 days after onset of vague abdominal pain
- CECT shows necrotizing pancreatitis, a luminal filling defect in the portal vein and formation of hilar collaterals. There are no prior CECTs available.
- The diagnosis of portal vein thrombosis is made

1. Would you treat this patient with anticoagulation?
- Yes, with therapeutic dose anticoagulation
- Yes, with prophylactic dose anticoagulation
- No

2. Would you perform upper endoscopy to screen for and eventually treat esophageal varices before starting anticoagulant therapy?
- Always
- Usually
- Sometimes
- Never

Repeat CECT was done after 5 days (figure 1F) and shows extension of the thrombus to the splenic vein (arrow pointing upwards) and expansion of the collateral pathway in the gastroepiploic veins along the great curvature of the stomach (arrow pointing downwards).

3. How would you treat this patient?
- Stay conservative (no therapeutic dose of anticoagulation)
- Start therapeutic dose of anticoagulation
- Continue therapeutic dose of anticoagulation
- Proceed to intervention

3a. if proceed to intervention, please specify

CHAPTER 5

Splanchnic vein thrombosis in necrotizing pancreatitis: *a post-hoc analysis of a nationwide prospective cohort*

HPB 2023

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ABSTRACT

Background: Treatment guidelines for splanchnic vein thrombosis in necrotizing pancreatitis are lacking due to a lack of data on the full clinical spectrum.

Methods: We performed a post-hoc analysis of a nationwide prospective necrotizing pancreatitis cohort. Multivariable analyses were used to identify risk factors and to compare the clinical course of patients with and without SVT.

Results: SVT was detected in 97 of the 432 included patients (22%) (median onset: 4 days). Risk factors were left, central, or subtotal necrosis (OR 28.49; 95% CI 20.09-40.40), right or diffuse necrosis (OR 5.75; 95% CI 3.89-8.50), and younger age (OR 0.99; 95% CI 0.98-1.00). Patients with SVT had higher rates of bleeding (n=10, 11%) and bowel ischemia (n=4, 4%) compared to patients without SVT (n=14, 4% and n=2, 0.6%; OR 3.24; 95% CI 1.27-8.23 and OR 7.29; 95% CI 1.31-40.40, respectively), and were independently associated with ICU admission (adjusted OR 2.53; 95% CI 1.37-4.68). Spontaneous recanalization occurred in 62% of patients (n=40/71). Radiological and clinical outcomes did not differ between patients treated with and without anticoagulants.

Discussion: SVT is a common and early complication of necrotizing pancreatitis, associated with parenchymal necrosis and younger age. SVT is associated with increased complications and a worse clinical course, whereas anticoagulation use does not appear to affect outcome.

INTRODUCTION

Splanchnic vein thrombosis (SVT) is a well-known complication of acute pancreatitis involving the splenic (SpIV), portal (PV) and/or superior mesenteric (SMV) vein (1-3). The exact incidence and pathophysiology remain unclear (4). Previous studies have demonstrated SVT in 2% to 51% of patients with acute pancreatitis, with the highest incidence in patients with necrotizing pancreatitis (1-3). Several mechanisms of SVT have been proposed in necrotizing pancreatitis, including local inflammatory infiltration, systemic inflammatory response, release of activated pancreatic enzymes, and extrinsic compression (5-7). Only a few studies have investigated the relationship between SVT and inflammatory markers, the location and extent of pancreatic parenchymal necrosis, the co-localization of such collections, and the presence of increased intra-abdominal pressure (8-13). These studies were mostly small (20 to 45 patients) and lacked a control group without SVT. In addition, there is a lack of data on the natural course of SVT following necrotizing pancreatitis, which may be due to imaging studies being guided by disease severity rather than systematical detection and evaluation of SVT. The timing of SVT onset and its evolution over time (i.e., resolution or progression) are particularly relevant, as these may have implications for (preventive) treatment, such as drainage of collections and therapeutic anticoagulation. Finally, it remains unclear whether SVT leads to worse clinical outcomes or whether the clinical course of patients with necrotizing pancreatitis depends mainly on the severity of the underlying disease. This uncertainty is driven by a serious risk of confounding in the currently available literature (8, 14-17).

We therefore performed the present study with the aim to determine the incidence, risk factors, natural course, and clinical outcomes of SVT in a large nationwide prospective cohort of patients with necrotizing pancreatitis. We also evaluated clinical and radiological outcomes associated with the use of therapeutic anticoagulation.

METHODS

Study design and population

This study was a post-hoc analysis of 639 patients with necrotizing pancreatitis included in the prospective nationwide registry of the Dutch Pancreatitis Study Group (DPSG). These patients were enrolled at 21 hospitals between 2004 and 2008 if they met the inclusion criteria of necrotizing pancreatitis, defined as a computed tomography severity index (CTSI) score of three or more, as assessed by a single expert pancreatic radiologist (TLB). For this study, patients were excluded if they had incomplete (follow-up) data or were lost to follow-up. All patients provided written

informed consent for the initial registration. Ethical approval by the medical ethical committee was waived for the current post-hoc analyses. This study was conducted according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines (18).

Data collection

Clinical data from the index admission for acute pancreatitis were collected prospectively using a predefined, standardized case record form. This included age, sex, etiology, American Society of Anesthesiologist (ASA) classification, medical history (including venous thromboembolism), previous use of therapeutic anticoagulants, body mass index (BMI), smoking status, and peak laboratory values (CRP and leukocytes) in the first 48 h. Computed tomography (CT) scans were collected from all participating hospitals and were re-evaluated by a single radiologist (TLB). If patients were transferred, CT scans were obtained from both hospitals. Due to the multicenter design, a variety of CT scanners were used, but all were 16-slice or higher multidetector scanners with slice thicknesses ranging from 1.5 to 3 mm. The CTSI score, the presence, extent and location of (peri)pancreatic necrosis and collections were assessed on the first CT performed 72 h after the onset of acute pancreatitis. Left-sided necrosis referred to pancreatic tail necrosis, right-sided necrosis referred to pancreatic head necrosis, central necrosis to pancreatic neck and/or body necrosis, subtotal necrosis to pancreatic neck, body, and most of head and tail necrosis, and diffuse necrosis to uni- or multifocal areas of necrosis throughout the pancreas. The extent of pancreatic parenchymal necrosis was visually estimated as less than 30%, between 30% and 50%, and greater than 50%. All contrast-enhanced CTs were reviewed for the presence, location, and extent of SVT were also assessed on each CT scan. Long-term follow-up data, and collection of data on several factors related to SVT and the use of therapeutic anticoagulation, were collected retrospectively until January 2020.

Outcome measures and definitions

The primary outcome was the occurrence of SVT, defined as an intraluminal filling defect in one or more of the splanchnic veins. Vein compression or stenosis without an actual thrombus and the presence of collaterals without a visible vein were not sufficient for the diagnosis of SVT. Thrombus location was divided into SpIV, PV, SMV, or a combination. The degree of thrombus was classified as occlusive (absence of flow) or non-occlusive (presence of flow). In the case of multiple affected vessels, scoring was pragmatically considered occlusive if one thrombus was occlusive and another was non-occlusive. Collateral circulation was defined radiologically as the presence of varices, collaterals, or cavernomas. Co-localized compression (i.e., due to (peri) pancreatic fluid collections or edema) was also assessed on the initial CT scan of SVT diagnosis. Other radiological outcomes included recanalization, time to recanaliza-

tion, thrombus progression, and SVT recurrence. Recanalization was defined as the absence of a thrombus in a previously thrombosed splanchnic vein(s), except for an obliterated vein as a result of persistent thrombotic occlusion. Progression to other splanchnic vein(s), to total occlusion, or both, was defined as thrombus progression. Clinical outcomes included pancreatitis-related mortality, (multiple) organ failure, intensive care unit (ICU) admission, and SVT-related complications such as bleeding and bowel ischemia. Therapeutic anticoagulants referred to any agent prescribed at a therapeutic dose, such as low-molecular-weight heparin, unfractionated heparin, and vitamin K antagonist. A summary of all definitions is provided in Table S1.

Statistical analysis

Statistical analysis was performed with SPSS for Windows (version 26.0) (19). Continuous variables were expressed as mean (standard deviation [SD]) or median (interquartile range [IQR]), whereas categorical variables were expressed as absolute numbers and percentages. The Student's T test or Mann-Whitney U test was used to compare continuous variables, and chi-square test, or in the case of small groups, Fisher's exact test was used for categorical data. Multivariable logistic regression analyses were used to assess independent predictive factors for the development of SVT. The pattern of pancreatic parenchymal necrosis was reduced to (1) no necrosis (reference), (2) left, central, or subtotal necrosis, and (3) right or diffuse necrosis because of the limited number of cases. The percentage of necrotic tissue was not included to avoid multicollinearity. Subgroup analyses were performed to compare clinical outcomes between patients with and without SVT. Multivariable analyses adjusted for potential confounders with the presence of SVT as the dependent variable were used to assess the independent effect of SVT on these clinical outcomes. Covariates were added on the basis of clinical reasoning. Subgroup analyses were also performed to compare the radiological and clinical outcomes of patients with SVT treated with and without therapeutic anticoagulants. Multiple imputation was used for missing data for variables with less than 20% missing values. Results are reported as (adjusted) odds ratios (OR) with 95% confidence intervals (CI). A p-value less than 0.05 was considered statistically significant.

RESULTS

Between 2004 and 2008, 639 patients were enrolled in the prospective cohort of necrotizing pancreatitis. Of this cohort, 432 patients were eligible for this study; 203 patients had incomplete data, 4 patients were lost to follow-up, and 1 patient had pancreatic cancer in the retrospective evaluation. Baseline characteristics are summarized in Table 1. The median age was 58 years (IQR 45-70), and 273 patients (63%) were male. The most common etiologies were biliary (n=205, 47%), alcoholic (n=96,

22%), and idiopathic (n=92, 21%). Nine patients (2%) had a previous history of venous thromboembolism, and 23 patients (5%) were on therapeutic anticoagulants. Pancreatic parenchymal necrosis, with or without extrapancreatic necrosis, was present in of 235 patients (54%), while 197 patients (46%) had extrapancreatic necrosis only.

Diagnosis

Of the 432 patients included, 97 patients (22%) developed SVT. The median time to diagnosis of SVT after admission for acute pancreatitis was 4 days (IQR 2-7; Table 2). SVT was detected on the first CT scan in 76 patients (78%), on the second CT scan in 17 patients (18%), and on the third or subsequent CT scan in 4 patients (4%). At diagnosis, isolated SpIV was the most commonly involved vessel (n=32, 33%), followed by the isolated PV (n=20, 21%) and the isolated SMV (n=15, 16%). Seven patients (7%) had triple vessel thrombosis. Non-occlusive thrombosis was observed in 73 patients (75%) and occlusive thrombosis in 24 patients (25%). Collateral circulation was present in 7 patients (7%), and co-localized venous compression in 6 patients (6%). Figure 1 shows the pattern of pancreatic parenchymal necrosis per affected vessel at the time of diagnosis.

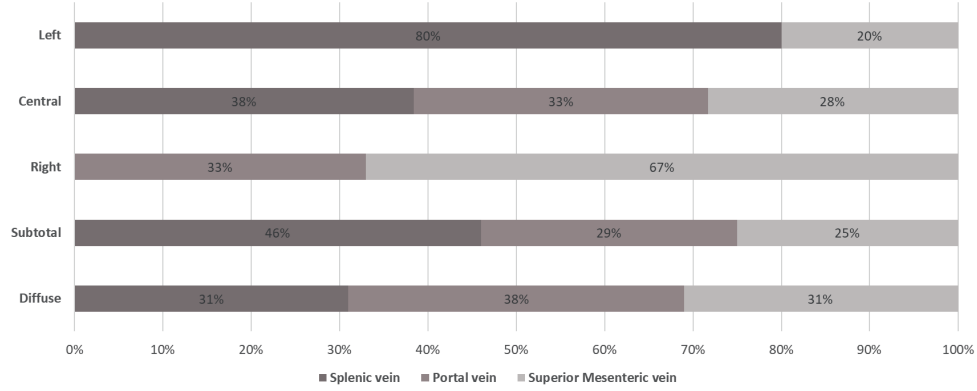

Figure 1. Pattern of pancreatic parenchymal necrosis per affected vessel

Risk factors

Univariable and multivariable analyses of risk factors for the development of SVT are shown in Table 3. Univariable analyses identified younger age, use of therapeutic anticoagulants on admission, a higher CRP level, left, central, or subtotal parenchymal necrosis, and right or diffuse parenchymal necrosis as risk factors. In multivariable analysis, left, central, or subtotal parenchymal necrosis (OR 28.49; 95% CI 20.09-40.40) and right or diffuse parenchymal necrosis (OR 5.75; 95% CI 3.89-8.50) were independently associated with the development of SVT, whereas higher age was a protective factor (OR 0.99 (95% CI 0.98-1.00).

Table 1. Patients and disease characteristics in 432 patients with necrotizing pancreatitis

	Overall (N = 432)	**No SVT (N = 335)**	**SVT (N = 97)**	**P-value**
Age (years)	58 (45-70)	59 (45-71)	56 (45-67)	0.072
Men	273 (63%)	215 (64%)	58 (60%)	0.430
Etiology				
Biliary	205 (47%)	164 (49%)	41 (42%)	0.245
Alcohol	96 (22%)	73 (22%)	23 (24%)	0.689
Idiopathic	92 (21%)	71 (21%)	21 (22%)	0.923
Other	39 (9%)	27 (8%)	12 (12%)	0.192
Medical history				
Cardiovascular (n=431)	165 (38%)	133 (40%)[a]	32 (33%)	0.223
VTE	9 (2%)	8 (2%)	1 (1%)	0.691
Pulmonary (n=430)	42 (10%)	35 (11%)[b]	7 (7%)	0.336
Chronic renal (n=430)	14 (3%)	12 (4%)[a]	2 (2%)[a]	0.745
Diabetes mellitus (n=431)	54 (13%)	47 (14%)	7 (7%)[a]	0.200
AC use at admission (n=425)	23 (5%)	21 (6%)[c]	2 (2%)[b]	0.127
ASA				
1	124 (29%)	90 (27%)	34 (35%)	0.117
2	246 (57%)	197 (59%)	49 (51%)	0.146
3	62 (14%)	48 (14%)	14 (14%)	0.979
4	0	0	0	-
BMI (n=214)	27 (25-31)	27 (25-31)[d]	26 (24-30)[e]	0.310
Smoking (n=123)	42 (34%)	32 (34%)[f]	10 (36%)[g]	0.842
Laboratory values[*]				
Leukocytes (n=395)	19 (15-23)	19 (15-22)[h]	19 (16-23)[i]	0.276
CRP (n=347)	301 (226-389)	293 (220-377)[j]	341 (223-437)[k]	0.012
Imaging severity				
CTSI	6 (4-8)	4 (4-6)	8 (6-10)	<0.001
Parenchymal necrosis	235 (54%)	145 (43%)	90 (93%)	<0.001
Right	9 (4%)	6 (4%)	3 (3%)	0.427
Left	26 (11%)	12 (8%)	14 (16%)	<0.001
Central	97 (41%)	54 (37%)	43 (48%)	<0.001
Subtotal	25 (11%)	7 (5%)	18 (20%)	<0.001
Diffuse	78 (33%)	66 (46%)	12 (13%)	0.098
Extent of necrosis				
<30%	96 (22%)	73 (22%)	23 (24%)	0.689
30-50%	67 (16%)	43 (13%)	24 (25%)	0.004
>50%	72 (17%)	29 (9%)	43 (44%)	<0.001
EXPN only	197 (46%)	190 (57%)	7 (7%)	<0.001

Data are presented as n (%) or median (IQR). Percentages may not total 100 because of rounding. Missing patients: a=1, b=2, c=5, d=171, e=47, f=240, g=69, h=31, i=6, k=11. [*]Highest value in the first 48 hours after admission. Abbreviations: AC anticoagulation, ASA American Society of Anesthesiologists, BMI body mass index, CRP c-reactive protein, CTSI computed tomography severity index, EXPN extrapancreatic necrosis, VTE venous thromboembolism.

Table 2. Radiological characteristics in 97 patients with splanchnic vein thrombosis

At the time of diagnosis	**Total (n=97)**
Time to diagnosis (days)	4 (2-7)
Number of CT scan with diagnosis	
First CT	76 (78%)
Second CT	17 (18%)
≥Third CT	4 (4%)
Anatomical location	
SpIV	32 (33%)
PV	20 (21%)
SMV	15 (16%)
SpIV + PV	11 (11%)
SpIV + SMV	5 (5%)
PV + SMV	7 (7%)
SpIV + PV + SMV	7 (7%)
Extent thrombosis	
Occlusive thrombosis	24 (25%)
Non-occlusive thrombosis	73 (75%)
Collateral circulation	9 (9%)
Co-localized compression	6 (6%)
At last imaging	**Total (n=88)***
Recanalization	50 (57%)
Time to recanalization (weeks)	4 (2-11)
Persistent thrombosis	38 (43%)
Anatomical location	
SpIV	23 (59%)
PV	7 (18%)
SMV	2 (5%)
SpIV + PV	5 (13%)
SpIV + SMV	0
PV + SMV	0
SpIV + PV + SMV	2 (5%)
Extent thrombosis	
Occlusive thrombosis	18 (46%)
Non-occlusive thrombosis	9 (23%)
Thrombotic obliteration	12 (31%)
Collateral circulation	25 (64%)
Radiologic follow-up (months)	10 (3-24)
CT scans per patients	7 (4-10)

*Data are presented as n (%) or median (interquartile range). Percentages may not total 100 because of rounding. *Follow-up imaging was missing in 9 out of 97 patients with splanchnic vein thrombosis. Abbreviations: CT computed tomography, PV portal vein, SMV superior mesenteric vein, SpIV splenic vein, SVT Splanchnic vein thrombosis.*

Table 3. Univariable and multivariable analyses: risk factors for developing splanchnic vein thrombosis (n=97)

	Univariable		Multivariable	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
Age	0.99 (0.98-0.99)	<0.001	0.99 (0.98-1.00)	<0.001
Male	0.83 (0.52-1.32)	0.431		
ASA ≥III	1.01 (0.53-1.92)	0.979		
AC use at admission[#]	0.39 (0.23-0.67)	0.001	0.63 (0.35-1.14)	0.124
Alcoholic etiology	1.11 (0.65-1.91)	0.689		
CRP[*,#]	1.00 (1.00-1.00)	<0.001	1.00 (1.00-1.00)	0.946
Leukocytes[¨,#]	1.01 (1.00-1.02)	0.208		
Pattern parenchymal necrosis				
Left, central, or subtotal	27.89 (19.95-38.98)	<0.001	28.49 (20.09-40.40)	<0.001
Right of diffuse	5.66 (3.86-8.29)	<0.001	5.75 (3.89-8.50)	<0.001

[*]Highest CRP in the first 48 hours after admission. [¨]Highest leucocytes in the first 48 hours after admission. [#]Missing data were imputed. Abbreviations: AC anticoagulation, ASA American Society of Anesthesiologists, CRP c-reactive protein, CTSI computed tomography severity index.

Clinical outcomes

Based on the cut-off between the 3rd and 4th quartile of the time to diagnosis of SVT, which is 7 days, we decided to report clinical outcomes that occurred beyond the first week after admission. During this first week, 7 patients (2%) died (n=5 patients without SVT and n=2 patients with SVT) and were therefore excluded from further analysis. The clinical outcomes of the remaining 425 patients are shown in Table 4. Of these, 55 patients (13%) died from pancreatitis-related causes. Persistent or new organ failure occurred in 154 patients (36%) and persistent or new multiple organ failure in 65 patients (15%). A total of 174 patients (41%) were hospitalized in the ICU after the first week. The median total hospital stay was 45 days (IQR 22-97). Bleeding occurred in 24 patients (6%), and bowel ischemia in 6 patients (1%). The median clinical follow-up period was 152 months (IQR 85-167). Univariable analysis showed a significant association between SVT and bleeding, with bleeding occurring more frequently in 10 patients with SVT (11%) compared to 14 patients without SVT (4%; OR 3.24; 95% CI 1.27-8.23; p=0.014) (Table S2). Spontaneous bleeding occurred in 5 patients with SVT versus 7 patients without SVT, and iatrogenic bleeding during or after invasive procedures (e.g., drainage, necrosectomy or other surgery) occurred in 5 patients with SVT versus 7 patients without SVT. The reported symptoms were gastrointestinal bleeding in 3 patients (melena in 1, hematemesis in 1, hematochezia in 1), intra-abdominal bleeding in 16 patients, combined gastrointestinal and intra-abdominal bleeding in 1 patients, clinical manifestations of bleeding in 2 patients, and unknown in 2 patients. None of the bleedings were related to gastroesophageal varices.

Bowel ischemia occurred in 4 patients with SVT (4%) compared to 2 patients without SVT (0.6%; OR 7.29; 95% CI 1.31-40.4; p=0.023). Three of these 4 patients had PV and/or SMV involvement, while the remaining patient developed abdominal compartment syndrome. Further details on bowel ischemia are provided in Table S3. Note that all patients with bowel ischemia in the SVT group died as a result of the ischemia. The limited number of events (n=24 for bleeding, n=6 for bowel ischemia) prevented multivariable analysis. Multivariable analysis adjusting for potential confounders on the clinical course showed no association between the presence of SVT and pancreatitis-related death and (multiple) organ failure (Table 4), but did show an association with a higher rate of ICU admission (OR 2.53; 95% CI 1.37-4.68; p=0.003).

Table 4. Multivariable comparison of clinical outcomes in patients with and without splanchnic vein thrombosis[*]

Outcome	Overall N = 425[^]	No SVT N = 330[a]	SVT N = 95[b]	Adjusted OR (95% CI)[#]	P-value
Pancreatitis-related death	55 (13%)	38 (12%)	17 (18%)	1.44 (0.64-3.26)	0.378
Organ failure	154 (36%)[c]	104 (32%)[c]	50 (53%)	0.88 (0.51-1.50)	0.636
Multiple organ failure	65 (15%)[c]	41 (12%)[c]	24 (25%)	1.17 (0.73-1.77)	0.584
ICU admission	174 (41%)	119 (36%)	57 (60%)	2.53 (1.37-4.68)	0.003
Total admission days	45 (22-97)	43 (22-96)	49 (30-100)	-	0.115

Data are presented as n (%) or median (IQR). [*]Clinical outcomes occurring 7 days after admission. [^]7 patients died in the first week ([a]=5 in no SVT group, [b]=2 in SVT group) and were therefore excluded for this analysis. Missing patients: c=1. [#]The covariates included per outcome are listed in the supplementary appendix (table S4). ~Assessed in univariable analysis. Abbreviations: ICU intensive care unit, SVT splanchnic vein thrombosis.

Therapeutic anticoagulation

Data on therapeutic anticoagulant treatment were available for 88 of the 97 patients with SVT (91%). Of these, 17 patients (19%) received therapeutic anticoagulation during their initial hospitalization, with two patients receiving anticoagulants prior to hospitalization (Table S5). In addition, therapeutic anticoagulation was initiated in six patients for indications other than SVT (n=3 pulmonary embolism, n=2 deep vein thrombosis, n=1 *de novo* atrial fibrillation). The initial anticoagulation regimen included therapeutic doses of low-molecular-weight heparin in 12 patients, a vitamin K antagonist in four patients, and unfractionated heparin in one patient. The duration of treatment varied from 1 to 12 months or more (n=12), to indefinite/end of follow-up (n=3). The duration of treatment was unclear in two patients. No significant differences were found between anatomical location, extent or progression of SVT, presence of collateral circulation, and whether patients were treated with therapeutic anticoagulants (Table S6). There was a trend towards a higher incidence of recanalization in patients who did not receive therapeutic anticoagulation (n=40/71,

62%) compared to those who did (n=6/17, 35%), although this was not statistically significant in univariable analyses (OR 0.34; 95% CI 0.11-1.04; p=0.052; Table S7). The median time to recanalization was similar between the groups (4 weeks (IQR 1-19) versus 3 weeks (IQR 3-9); p=0.728). The incidence of bleeding and bowel ischemia was also similar. Among patients on anticoagulants, 2 experienced bleeding (12%) and none experienced bowel ischemia. Among patients not on anticoagulants, 8 experienced bleeding (12%) and 4 experienced bowel ischemia (6%).

Radiologic follow-up

Follow-up imaging was available for 88 out of 97 patients (91%), with a median follow-up period of 10 months (IQR 3-24) and a median of 7 CT scans (IQR 4-10; Table S8). Recanalization was observed in 49 patients (56%) after a median of 4 weeks (IQR 2-11) (Table 2). In the 39 patients with persistent SVT, SpIV remained the most frequently involved vessel (n=23, 59%). The prevalence of thrombosis decreased by 90% and 66% for the SMV and PV, respectively, while the decrease for the SpIV was 42% (Figure S1). Compared to the first CT scan, more patients with persistent SVT had occlusive thrombosis (n=18, 46%) or vein obliteration (n=12, 31%) with collateral circulation (n=25, 64%) at the last scan. Thrombus progression was observed in 13 patients (14%), and one patient (1%) developed recurrent SVT. In univariable analysis (Table 5), SpIV thrombosis (OR 4.77 ;95% CI 1.83-12.46), occlusive thrombosis at diagnosis (OR 11.50; 95% CI 3.34-38.31), and thrombus progression (OR 22.62; 95% CI 2.78-183.70) were significantly risk factors for recanalization failure, whereas SMV thrombosis (OR 0.31; 95% CI 0.12-0.82) was a protective factor.

Table 5. Univariable analysis: risk factors for failure of recanalization (n=38)

	Univariable	
	OR (95% CI)	**P-value**
Age	1.00 (0.97-1.03)	0.961
Male sex	1.14 (0.48-2.72)	0.763
AC use[#]	2.93 (0.96-8.93)	0.058
SpIV thrombosis	4.77 (1.83-12.46)	<0.001
PV thrombosis	0.88 (0.38-2.05)	0.761
SMV thrombosis	0.31 (0.12-0.82)	0.017
Triple vessel thrombosis	1.84 (0.39-8.78)	0.443
Occlusive thrombosis	11.50 (3.45-38.31)	<0.001
Thrombus progression	22.62 (2.78-183.70)	<0.001
Timing of SVT (days)	0.99 (0.95-1.02)	0.424

[#]Missing data were not imputed. Abbreviations: AC anticoagulation, PV portal vein, SMV superior mesenteric vein, SpIV splenic vein.

DISCUSSION

This study represents one of the largest multicenter prospective cohorts of patients with necrotizing pancreatitis with long-term follow-up and showed an overall incidence of splanchnic vein thrombosis (SVT) of 22%. Pancreatic parenchymal necrosis, with a higher risk for left, central, or subtotal necrosis than for right or diffuse necrosis, and younger age were identified as independent risk factors for SVT. SVT is associated with higher rates of bleeding and bowel ischemia, and has an impact on ICU admission. Spontaneous recanalization was observed in more than 60% of patients. Therapeutic anticoagulation was infrequently administered and did not appear to affect radiological and clinical outcomes.

To our knowledge, the only other high-volume study reported a 50% incidence of SVT in patients with necrotizing pancreatitis (20). This higher rate may be due to a different definition combining intraluminal filling defect, presence of collaterals, and non-visualization of the vein. Furthermore, this cohort from a single tertiary center probably included more severely ill patients, leading to a possible overestimation. The median time to diagnosis found in our study was as early as 4 days, which could be even earlier depending on the timing of the first CT scan. This timing differed from previous reports, which reported a median of up to 17 days or several weeks (8, 21-23). The design of these studies may have resulted in delayed diagnosis due to the lack of early imaging studies performed at the referring hospitals. This is supported by the presence of collaterals at the time of diagnosis in more than one third of patients (23), compared to 7% in our study.

Factors contributing to the development of venous thrombosis are described in the Virchow's triad: stasis, endothelial injury, and hypercoagulability (24). Previous studies in necrotizing pancreatitis have suggested that stasis due to mechanical compression, as indicated by co-localized collections, is an important mechanism (9, 11). However, in our study, co-localized compression was often not seen at the time of diagnosis. This is consistent with a previous study showing that the organization of fluid collections typically takes several weeks (25). As secondary infection of (peri)pancreatic necrosis is also a relatively late manifestation of necrotizing pancreatitis (25, 26), we did not include both variables in the multivariable regression model. Nevertheless, we found that pancreatic parenchymal necrosis, as opposed to extrapancreatic necrosis, was the most significant independent risk factor for the development of SVT, with an OR of 28.49 for left, central, or subtotal necrosis and an OR of 5.75 for right or diffuse necrosis. Systemic inflammation markers such as CRP and leukocytes were not identified as risk factors. This suggests that local inflammatory infiltration, subsequently leading to direct endothelial injury, may play a primary role in the pathophysiology,

rather than systemic inflammation. This hypothesis is supported by the predominant involvement of the splenic vein that we and others have observed (8-10, 16, 22, 23, 27). The course of the SpIV along the pancreatic tail and body may explain why left-sided and centrally located parenchymal necrosis was found to be an independent risk factor. In addition, a previous study reported an almost threefold and eightfold higher incidence of SVT in patients with necrotizing pancreatitis, as compared to deep venous thromboembolism and pulmonary embolism (20). However, an unexpected finding was the significant association between SVT and a younger age. This may have been influenced by differences between the younger and older populations, such as BMI, nicotine use and etiology, whereas (time to) mortality did not show any differences (data not shown).

Previous research has suggested that timely drainage of (infected) necrotic collections may prevent the development of SVT (9, 11, 16), although this has not been extensively studied. Based on our observations that SVT is a very early complication and that no modifiable risk factors have been identified, we would not recommend a proactive drainage strategy to prevent of SVT. Another argument supporting this notion is that collections at this early stage are often not yet ''drainable". The question is whether drainage could improve the prognosis of SVT by reducing the exposure of the splanchnic vein to local inflammation. Our study shows that spontaneous recanalization occurs in over 60% of patients within a median of 3 weeks, probably with prophylactic dose anticoagulation.

A rational treatment for SVT when extrapolating from other venous thromboses is the administration of therapeutic anticoagulants. However, the current evidence-based guideline for the management of acute pancreatitis (28) withholds on recommendations due to a lack of high-quality studies (29-32). Therapeutic anticoagulants aim to prevent thrombus progression and recurrence to avoid complications such as portal hypertension and bowel ischemia, but carry an inherent risk of bleeding (33-36). While a recent survey by our group showed that the majority of pancreatologists prescribe therapeutic anticoagulants for SVT (37), our cohort had a low treatment rate (19%), which may be related to the fact that we included only patients with necrotizing pancreatitis. We found similar, albeit significant, rates of bleeding and bowel ischemia in patients treated with and without therapeutic anticoagulants. In order to avoid unnecessary treatment, it seems essential to identify those patients who are at higher risk of insufficient recanalization and thus more susceptible to potential complications. A previous study found that a higher CTSI, increased abdominal pressure, and SMV involvement were significant risk factors for the development of symptomatic SVT (38). In this study, thrombus progression, occlusive thrombosis, and SpIV thrombosis were found to be significant risk factors for insufficient recanalization in univariable

analysis. Although limited by the small number of patients with failed recanalization (n=38), this supports the idea of a targeted symptom-driven anticoagulation strategy rather than a universal approach (39).

A recent study proposed a selective regimen for patients with acute pancreatitis, reserving therapeutic anticoagulation for those with PV and SMV thrombosis, and progressive SpIV thrombosis (40). This study found a significantly higher recanalization rate in the former group (67%) compared to the latter group (18%), which is consistent with our findings. Of note, the number of patients with progressive SpIV thrombosis in this study was limited (n=11). Nevertheless, the reported recanalization rate in 63 patients with PV or SMV thrombosis after a median of 30 days was substantially higher than previously reported for the total population (29). These findings highlight the importance of further investigation of a targeted anticoagulation strategy, ideally in a prospective study with a control group not receiving anticoagulants. Based on our findings, we recommend that the site and extent of thrombosis be considered in future anticoagulation strategies.

When deciding on anticoagulant therapy, it is important to consider the patient's overall prognosis. Several studies have reported an association between acute pancreatitis patients diagnosed with SVT and worse clinical outcomes, including mortality (14, 15, 17), organ failure (8, 16), ICU admission (8, 17), admission days (8, 14, 15), discharge location (15), and readmissions (15). However, these studies did not adequately adjust for potential confounders, such as disease severity, or differentiate between baseline characteristics and actual outcomes. In our study, we performed multivariable analyses specifically focusing on the independent effect of SVT on mortality, organ failure, and ICU admission occurring after SVT diagnosis. We observed an independent association with new or continued ICU admission beyond one week after admission. We also observed higher rates of bleeding and bowel ischemia in patients with SVT compared with those without. However, due to the limited number of events, we were unable to adjust for covariates related to disease severity and therapeutic anticoagulation, and caution should be exercised in interpreting these results. We hypothesize that bleeding in the SVT group may be due to a more severe disease course (e.g., bleeding from pseudoaneurysm or iatrogenic bleeding resulting from more frequently performed interventions) rather than being directly caused by SVT itself. Notably, none of the bleeding events were associated with portal hypertension, even in the long term, and there were no differences in bleeding rates based on the use of therapeutic anticoagulation. Careful attention to collaterals, especially in the retroperitoneum or along the gastric wall, seems to be important in pre- and perioperative management. Bowel ischemia proved to be a major complication, leading

to death in all but one patient. Of the patients with SVT, 75% had portal or superior mesenteric vein involvement.

This study has several limitations. First, a substantial proportion of patients were excluded from the study because of incomplete follow-up data. This was mostly due to the transition from paper-based to electronic medical records. Second, there were missing data on some baseline characteristics, such as BMI and smoking, and on outcomes. Data on the in-hospital prescription of therapeutic anticoagulants were collected post hoc and only for patients with SVT. Third, the small number of patients receiving therapeutic anticoagulation limited a thorough assessment of its efficacy and safety. Moreover, it is likely that confounding by indication may have occurred because our study did not have a randomized design. Therefore, the data on anticoagulation are not robust enough to make recommendations. Fourth, we mainly analyzed SVT as one and the same entity (regardless of size, extent, and location). This may have influenced clinical outcomes and the effect of anticoagulation. The exclusion of luminal narrowing without a filling defect as a diagnostic criterion for splanchnic vein thrombosis may also have influenced clinical outcomes. Another factor influencing clinical outcomes is that our cohort consists of patients from the era of open surgical necrosectomy (2004-2008). After the publication of the PANTER trial in 2010 (41), which demonstrated the superiority of the minimally invasive step-up approach, the latter has become the standard of care. However, in the absence of (pharmacological) strategies to reduce disease severity, we believe that our data on the incidence, risk factors, and natural course of SVT are generalizable to the current necrotizing pancreatitis population. In fact, this relatively old cohort offers a complete radiologic evaluation of necrotizing pancreatitis (e.g., all CTs, including CTs performed at referring centers, were obtained and re-evaluated from each patient, even during long-term follow-up).

CONCLUSION

SVT occurs within the first 4 days of diagnosis, affecting nearly one in four patients with necrotizing pancreatitis, and resolves spontaneously in more than half of the patients. Independent risk factors for SVT include pancreatic parenchymal necrosis, with left, central, or subtotal necrosis being the most at-risk pattern, and younger age. SVT is associated with higher complication rates and shows an independent association with ICU admission. To optimize treatment strategies, future research should focus on identifying patients with SVT who remain free of complications and achieve recanalization without the use of therapeutic anticoagulation, and vice versa.

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Supplementary table S1. Definitions

Baseline	
Acute pancreatitis	When two of the following criteria were met: upper abdominal pain, serum lipase concentration (or amylase) ≥ 3 times higher than the upper limit of normal or features of acute pancreatitis on imaging
Pancreatic parenchymal necrosis	Diffuse or focal area(s) of non-enhancing pancreatic parenchyma as detected on contrast enhanced CT (CECT)
Right-sided necrosis	Lack of enhancement primarily in the pancreatic head
Left-sided necrosis	Lack of enhancement primarily in the pancreatic tail
Central gland necrosis	Lack of enhancement primarily in the pancreatic neck and/or body
Subtotal necrosis	Lack of enhancement in pancreatic neck, body and greater part of pancreatic head and tail
Diffuse necrosis	Lack of enhancement in uni- or multifocal area(s) throughout the pancreas
Extrapancreatic necrosis	Persistent peripancreatic fluid collections on contrast enhanced computed tomography (CECT) in the absence of pancreatic parenchymal non-enhancement
Splanchnic vein thrombosis	Intraluminal filling defect of the splenic, portal and/or superior mesenteric vein on CECT
Collateral circulation	One of the following: a) varices or b) collaterals or c) cavernoma
Obliteration	Non-visualization of an initially thrombosed splanchnic vein(s), with previous CECTs showing a persistent thrombosis
Progression	Progression into other splanchnic vein(s), into total occlusion, or both
Recanalization	Absence of thrombosis in an initially thrombosed splanchnic vein(s), except for an obliterated vein as a result of a persistent thrombosis
Clinical outcomes	
Bleeding	Bleeding requiring surgical, radiologic or endoscopic intervention
Bowel ischemia	Bowel ischemia requiring a surgical intervention
Organ failure	No organ failure is assumed in the absence of lab and/or information in the discharge letter and/or notes. Definitions are adapted from the Atlanta classification and the same as previously used in the PANTER trial
Cardiovascular	Systolic blood pressure < 90 mmHg despite adequate fluid resuscitation or need for vasopressor support
Pulmonary	PaO2 < 60 mmHg despite FiO2 30%, or the need for mechanical ventilation
Renal	Serum creatinine > 177 mmol/L after rehydration or need for hemofiltration or haemodialysis
Multiple organ failure	Failure of 2 or more organ systems on the same day

Supplementary table S2. Univariate comparison of clinical outcomes in patients with and without splanchnic vein thrombosis[*]

Outcome	Overall N = 425[^]	No SVT N = 330[a]	SVT N = 95[b]	OR (95% CI)	P-value
Pancreatitis related death	55 (13%)	38 (12%)	17 (18%)	1.68 (0.90-3.13)	0.103
Organ failure	154 (36%)[c]	104 (32%)[c]	50 (53%)	2.38 (1.50-3.79)	<0.001
Multiple organ failure	65 (15%)[c]	41 (12%)[c]	24 (25%)	2.35 (1.35-4.19)	0.003
Bleeding	24 (6%)[c]	14 (4%)	10 (11%)[c]	3.24 (1.27-8.23)	0.014
Bowel ischemia	6 (1%)[c]	2 (0.6%)	4 (4%)[c]	7.29 (1.31-40.4)	0.023
ICU admission	174 (41%)	119 (36%)	57 (60%)	2.71 (1.69-4.32)	<0.001
Total admission days	45 (22-97)	43 (22-96)	49 (30-100)	-	0.115

Data are presented as n (%) or median (IQR). [*]Clinical outcomes occurring 7 days after admission. [^]7 patients died in the first week ([a]=5 in no SVT group, [b]=2 in SVT group) and were therefore excluded for this analysis. Missing patients: c=1. Abbreviations: ICU intensive care unit, SVT splanchnic vein thrombosis.

Supplementary table S3. Bowel ischemia per individual patient

	Time diagnosis (days)[a]	SVT Location	SVT extent	Time most recent CT scan (days)[b]	Surgical operation	Mortality
Patient with splanchnic vein thrombosis						
1	16	Splenic vein	Occlusive	1	Non-operable. Autopsy: colon ischemia	Yes
2	41	Splenic vein Portal vein	Occlusive Non-occlusive	2	Non-operable. Autopsy: small bowel ischemia with pneumatosis	Yes
3	10	Sup. mesenteric vein	Non-occlusive	1	Ischemic colon requiring subtotal colectomy with end ileostomy	Yes
4	3	Sup. mesenteric vein	Non-occlusive	3	Small bowel ischemia requiring ileum resection with end ileostomy	Yes
Patients without splanchnic vein thrombosis						
1	N/A	N/A	N/A	N/A	Ischemic colon requiring transverse colectomy	No
2	N/A	N/A	N/A	N/A	Ischemic cecum requiring cecum resection with end ileostomy	Yes

[a]Time between diagnosis of splanchnic vein thrombosis and occurrence of bowel ischemia. [b]Time between occurrence of bowel ischemia and most recent CT scan. Abbreviations: CT Computed tomography, SVT Splanchnic vein thrombosis.

Supplementary table S4. Confounders per variable in the multivariate logistic regression model of clinical outcomes

Pancreatitis-related death *After 7 days*	Presence of splanchnic vein thrombosis, age, male sex, ASA classification ≥3, presence of pancreatic parenchymal necrosis >50%, occurrence of infected necrosis before 7 days, occurrence of organ failure before 7 days, occurrence of abdominal compartment syndrome before 7 days
(Multiple) organ failure *Either new-onset (multiple) organ failure after 7 days or ongoing (multiple) organ failure*	Presence of splanchnic vein thrombosis, age, male sex, ASA classification ≥3, presence of pancreatic parenchymal necrosis >50%, occurrence of infected necrosis before 7 days, occurrence of abdominal compartment syndrome before 7 days
ICU-admission *Either new ICU-admission after 7 days or ongoing ICU-admission*	Presence of splanchnic vein thrombosis, age, male sex, ASA classification ≥3, presence of pancreatic parenchymal necrosis >50%, occurrence of infected necrosis before 7 days, occurrence of organ failure before 7 days, occurrence of abdominal compartment syndrome before 7 days

Abbreviations: ASA American Society of Anaesthesiologists, ICU intensive care unit.

Supplementary table S5. Details on treatment with therapeutic anticoagulation

Patient	Indication	Agent	Duration
1	splanchnic vein thrombosis	LMWH à VKA	≥12 months
2	splanchnic vein thrombosis	LMWH	~1 month (until death)
3	splanchnic vein thrombosis	LMWH	unknown
4	de novo atrial fibrillation	LMWH à VKA	indefinite
5	splanchnic vein thrombosis	heparin	~2 months
6	splanchnic vein thrombosis	LMWH à VKA	~4 months
7	pulmonary embolism	LMWH à VKA	~5 months
8	pulmonary embolism	LWMH	unknown
9	splanchnic vein thrombosis	LMWH à VKA	~6 months
10	splanchnic vein thrombosis	VKA	~6 months
11	prior outpatient use (atrial fibrillation)	VKA	indefinite
12	deep vein thrombosis	LMWH à VKA	≥5 months
13	prior outpatient use (atrial fibrillation)	VKA	indefinite
14	splanchnic vein thrombosis	VKA	~3 months
15	pulmonary embolism	LWMH à VKA	~5 months
16	splanchnic vein thrombosis	LMWH	~1 month (until death)
17	deep vein thrombosis	LMWH à heparin	~1 month (until death)

≥*Greater than or equal to. ~More or less. Abbreviations: LMWH low molecular weight heparin, VKA vitamin K antagonist.*

Supplementary table S6. Characteristics of splanchnic vein thrombosis in 88 patients treated with or without therapeutic anticoagulation*

6a. Anatomical location

	SpIV (n=30)	**PV (n=15)**	**SMV (n=13)**	**SpIV+PV (n=11)**	**SpIV+SMV (n=5)**	**PV+SMV (n=7)**	**SpIV+PV+SMV (n=7)**
AC (n=17)	6 (20%)	3 (20%)	3 (23%)	1 (9%)	1 (20%)	1 (14%)	2 (29%)
No AC (n=71)	24 (80%)	12 (80%)	10 (77%)	10 (91%)	4 (80%)	6 (86%)	5 (71%)
P-value	0.907	0.941	0.710	0.684	1.000	1.000	0.616

6b. Extent thrombosis and collateral circulation at diagnosis, and thrombus progression over time

	Occlusive thrombosis (n=25)	**Non-occlusive thrombosis (n=63)**	**Collateral circulation (n=7)**	**Thrombus progression (n=12)**
AC (n=17)	7 (28%)	10 (16%)	1 (14%)	5 (42%)
No AC (n=71)	18 (72%)	53 (84%)	6 (86%)	7 (58%)
P-value	0.235	0.235	1.000	0.115

*Data are presented as n (%). *Anticoagulation status was missing in 9 out of 97 patients with splanchnic vein thrombosis. Abbreviations: AC anticoagulation, PV portal vein, SMV superior mesenteric vein, SpIV splenic vein.*

Supplementary table S7. Outcomes in 88 patients with splanchnic vein thrombosis treated with or without anticoagulation[*]

Outcome	AC (n=17)	No AC (n=71)	OR (95% CI)	P-value
Recanalization	6 (35%)	40 (62%)[a]	0.34 (011-1.04)	0.052
Time to recanalization (weeks)	4 (1-19)	3 (3-9)[a]	-	0.728
Bleeding	2 (12%)	8 (12%)[b,c]	1.00 (0.19-5.21)	1.000
Bowel ischemia	0	4 (6%)[b, c]	-	0.579

Data are presented as n (%) or median (IQR). [*]Anticoagulation status was missing in 9 out of 97 patients with splanchnic vein thrombosis. [a]Follow-up imaging was missing in 6 patients. [b]2 patients died in the first week and were therefore excluded for this analysis. [c]1 patient had missing data. Abbreviations: AC anticoagulation.

Supplementary table S8. Natural* course of splanchnic vein thrombosis in 97 patients

Pt	CT 1ˇ	CT 2	CT 3	CT 4	CT 5	CT 6	CT 7	CT 8
1^	total SpIV partial SMV	total SpIV partial SMV	total SpIV	total SpIV	total SpIV			
2	partial PV	partial PV	-	-	-			
3	partial SpIV partial PV partial SMV	partial SpIV partial PV	-	-	-	-	-	
4	partial SpIV partial PV	partial SpIV partial PV	partial SpIV	total SpIV#	total SpIV	total SpIV	total SpIV	total SpIV
15	total SpIV	total SpIV	total SpIV	total SpIV	total SpIV#			
25	partial PV	-	-	-	-	-	-	
32	partial SMV	partial SMV	-	-				
39	partial PV	-	-					
57^	total SpIV	total SpIV partial PV	total SpIV partial PV	total SpIV	total SpIV			
58	partial SpIV	total SpIV	total SpIV	total SpIV#	total SpIV	total SpIV		
66	partial SpIV	partial SpIV	total SpIV	total SpIV#	total SpIV			
69^	partial PV	partial PV	total SpIV total PV	total SpIV total PV	total SpIV total PV	total SpIV total PV	total SpIV total PV	total SpIV total PV
74	partial SMV	partial SMV	partial SMV	partial SMV	-	-		
87	total SpIV partial PV	total SpIV partial PV	total SpIV partial PV					
92	partial SpIV	partial SpIV	partial SpIV	-	-	-	-	
96^	partial SpIV	-	-	-	-			
97	partial PV	partial PV	partial PV	-	-	-	-	
98	partial PV	partial PV	partial PV	partial PV	partial PV	partial PV	partial PV	partial PV
100	partial SpIV partial PV	partial PV	total SpIV partial PV	total SpIV# partial PV	total SpIV	total SpIV	total SpIV	total SpIV
105	total SpIV	total SpIV	total SpIV					
118	total SpIV	total SpIV	total SpIV	total SpIV	total SpIV	total SpIV		
123	partial SpIV	partial SpIV	-	-	-			
125	partial SpIV partial SMV	partial SpIV partial SMV	partial SpIV partial SMV	partial SMV	-	-	-	-
131	total SpIV partial SMV	total SpIV partial SMV	-	-	-	-	-	-
144^	partial PV partial SMV	partial PV partial SMV	-	-	-	-	-	-
149^	partial SpIV	partial SpIV	total SpIV partial PV	total SpIV partial PV	-	-		

CT 9	CT 10	CT 11	CT 12	CT 13	CT 14	CT 15	CT 16	CT 17
total SpIV	total SpIV	total SpIV	total SpIV					
total SpIV total PV								
partial PV total SpIV	partial PV total SpIV	partial PV total SpIV	partial PV total SpIV	total SpIV	total SpIV			
-	-							
-	-	-						
-	-	-	-	-	-	-		

Supplementary table S8. Natural* course of splanchnic vein thrombosis in 97 patients (*continued*)

150	total SpIV	total SpIV partial PV	total SpIV partial PV	total SpIV# partial PV	total SpIV totial PV	total SpIV totial PV	total SpIV totial PV	total SpIV totial PV
154	partial SpIV partial PV	partial PV						
156	total SpIV	total SpIV	total SpIV					
185	partial PV	partial PV	partial PV	partial PV	partial PV			
198	partial PV	-						
199^	total SpIV partial PV partial SMV	total SpIV partial PV partial SMV	total SpIV partial PV partial SMV	total SpIV	total SpIV#	total SpIV	total SpIV	total SpIV
201^	partial SMV	-	-	-				
221	total SpIV partial PV partial SMV	total SpIV partial PV partial SMV	total SpIV partial PV partial SMV	total SpIV partial PV partial SMV	total SpIV partial PV partial SMV	total SpIV partial PV partial SMV	total SpIV partial PV partial SMV	
228	partial SpIV	partial SpIV	total SpIV	total SpIV	total SpIV	total SpIV#	total SpIV	total SpIV
261	partial PV partial SMV	partial PV partial SMV	-	-				
262	partial SpIV partial PV	-	-	-				
269	partial PV	-						
277	partial SMV	partial SMV	-	-	-	-	-	-
285^	partial PV	partial PV	partial PV	partial PV	total PV	total PV	total PV	
289	partial PV							
296	partial PV	partial PV	partial PV	partial PV	partial PV	partial PV	partial PV	partial PV
303^	partial PV	partial PV	partial PV	partial PV	partial PV	partial PV	partial PV	partial PV
305	partial PV	partial PV	partial PV	partial PV	partial PV	partial PV	-	-
317	partial PV partial SMV	partial PV	-	-	-	-	-	-
331	partial SpIV partial PV partial SMV	partial SpIV partial PV partial SMV	-	-	-	-	-	partial PV
335	total SpIV partial PV	total SpIV partial PV						
340	partial PV							
342	total SpIV	total SpIV	total SpIV	total SpIV	total SpIV	total SpIV	total SpIV#	
344	partial PV partial SMV	partial PV partial SMV	partial PV	partial PV	-	-	-	-
346	partial SMV	partial SMV	partial SMV	partial SMV	partial SMV	partial SMV		
354	partial SpIV	partial SpIV	-	-	-	-	-	-
355	partial SMV	partial SMV	-	-	-	-	-	-

total SpIV totial PV	total SpIV totial PV	total SpIV totial PV	total SpIV totial PV
total SpIV	total SpIV	total SpIV	
-	-	-	
partial PV partial PV	partial PV	-	-
-	-	-	-
-	-		
-			
-	-	-	-
-	-	-	-

Supplementary table S8. Natural* course of splanchnic vein thrombosis in 97 patients (*continued*)

359	partial SpIV	-	-	-				
374^	total SpIV	total SpIV	total SpIV	total SpIV	total SpIV	total SpIV	total SpIV	total SpIV
376	total SpIV	-	-	-	-	-		
380	partial SMV	partial SMV	-	-	-			
384	partial PV	partial PV	-	-	-	-	-	-
385^	total SpIV partial PV partial SMV	total SpIV partial PV partial SMV	total SpIV partial PV partial SMV	total SpIV partial PV partial SMV	total SpIV partial PV partial SMV	total SpIV partial PV	total SpIV partial PV	total SpIV partial PV
394	total SpIV	total SpIV#	total SpIV	total SpIV	total SpIV			
395	partial SpIV partial SMV	partial SpIV partial SMV	partial SpIV partial SMV	-	-	-	-	-
420	partial SMV	-	-	-	-	-	-	-
434^	total SpIV	total SpIV	total SpIV	total SpIV				
448	partial SpIV	partial SpIV	partial SpIV	-	-	-	-	-
449	partial PV							
450	partial SpIV partial PV partial SMV	partial SpIV partial PV	partial PV	partial PV	partial PV	partial PV	partial PV	partial PV
457	partial SpIV	-	-	-	-			
459	partial PV partial SMV	partial PV partial SMV	partial PV partial SMV	partial PV partial SMV	partial PV partial SMV	partial SMV	partial SMV	-
467	partial SpIV partial SMV	-	-	-	-	-	-	-
473	partial SpIV partial PV	partial SpIV partial PV	-	-	-	-	-	-
478^	partial SMV	partial PV partial SMV	partial PV partial SMV	partial PV partial SMV	partial PV partial SMV	partial PV	partial PV#	
485	partial PV	partial PV	partial PV	-	-			
488	partial SpIV partial PV	partial SpIV partial PV	-	-				
490	partial SMV	-	-	-	-	-	-	
496	partial SpIV							
506	partial PV partial SMV	partial PV partial SMV	partial PV partial SMV	partial PV partial SMV	partial PV partial SMV	partial PV	partial PV	partial PV
509	total SpIV total PV	total SpIV total PV	total SpIV total PV					
512	partial SpIV							
514^	partial SpIV	-	-	-	-	-	-	-

total SpIV

-

- - -

-

- -

partial PV partial PV partial PV partial PV partial PV partial PV partial PV partial PV

- - - - - - - - -

- -

- -

partial PV partial PV partial PV - - -

Supplementary table S8. Natural* course of splanchnic vein thrombosis in 97 patients (*continued*)

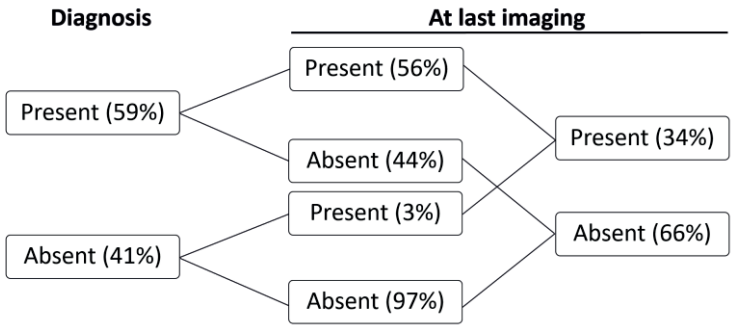
521	partial SMV	-	-	-	-	-	-	-
529	partial SpIV	-	-	-	-	-	-	
532	partial SpIV partial PV partial SMV	partial SpIV partial PV partial SMV						
535	partial PV	partial PV	-	-	-	-	-	-
538	partial PV	partial PV	partial PV	-	-	-	-	
539	total SpIV							
574	partial SpIV	partial SpIV						
583	partial SMV							
584	partial SpIV	total SpIV	total SpIV#	total SpIV	total SpIV	total SpIV	total SpIV	
592	total PV total SMV							
599	partial SMV	-						
600	partial SpIV	partial SpIV	partial SpIV	partial SpIV	partial SpIV	partial SpIV	partial SpIV	partial SpIV
603	partial SpIV	partial SpIV	-	-				
619	total SpIV partial PV	total SpIV	total SpIV	total SpIV	total SpIV	total SpIV	total SpIV	total SpIV
620^	partial SMV	partial SMV	partial SMV	partial SMV	partial SMV			
625	partial SMV							
627^	total SpIV partial PV	total SpIV partial PV	total SpIV partial PV	total SpIV	total SpIV			
638	total SpIV	total SpIV	total SpIV	total SpIV	total SpIV	total SpIV		

**17 out of 88 patients with a known anticoagulation status used anticoagulants. ˜CT 1= the first contrast-enhanced computed tomography that confirmed splanchnic vein thrombosis. #Obliterative vein from this CT onward. ^Patients on anticoagulation. Abbreviations: partial non-occlusive thrombosis, PV portal vein, SMV superior mesenteric vein, SpIV splenic vein, SVT Splanchnic vein thrombosis, total occlusive thrombosis.*

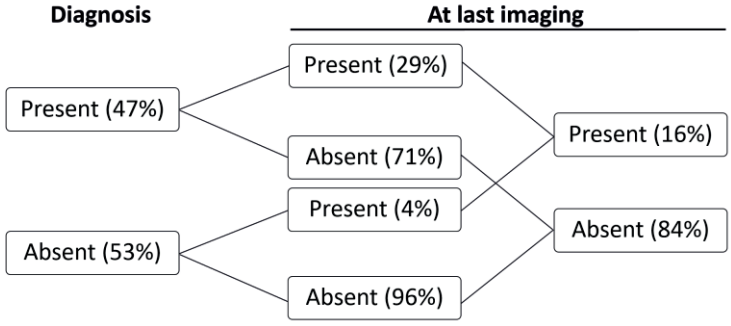
- - - -

total SpIV total SpIV total SpIV total SpIV total SpIV#

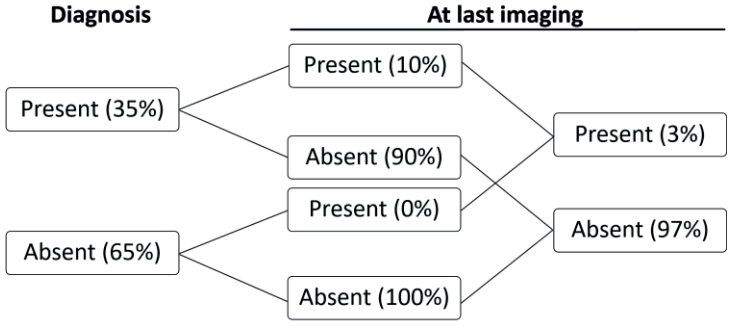
a) Splenic vein



b) Portal vein



c) Superior mesenteric vein



Supplementary figure S1. Outcome of obstruction per affected vessel compared to the initial diagnosis
Undertext: The decrease in prevalence of splanchnic vein thrombosis corresponds to the difference in obstructed venous segments between diagnosis and last imaging.

PART III

Prevention of recurrent acute pancreatitis

CHAPTER 6

Development of pancreatic diseases during long-term follow-up after acute pancreatitis: *a post-hoc analysis of a prospective multicenter cohort*

Journal of Gastroenterology and Hepatology 2024

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ABSTRACT

Background and objective: More insight into the incidence of and factors associated with progression following a first episode of acute pancreatitis (AP) would offer opportunities for improvements in disease management and patient counseling.

Methods: A long-term post-hoc analysis of a prospective cohort of patients with AP (2008–2015) was performed. Primary endpoints were recurrent acute pancreatitis (RAP), chronic pancreatitis (CP), and pancreatic cancer. Cumulative incidence calculations and risk analyses were performed.

Results: Overall, 1,184 patients with a median follow-up of 9 years (IQR: 7–11) were included. RAP and CP occurred in 301 patients (25%) and 72 patients (6%), with the highest incidences observed for alcoholic pancreatitis (40% and 22%). Pancreatic cancer was diagnosed in 14 patients (1%). Predictive factors for RAP were alcoholic and idiopathic pancreatitis (OR 2.70, 95% CI 1.51–4.82 and OR 2.06, 95% CI 1.40–3.02), and no pancreatic interventions (OR 1.82, 95% CI 1.10–3.01). Non-biliary etiology (*alcohol*: OR 5.24, 95% CI 1.94–14.16, *idiopathic*: OR 4.57, 95% CI 2.05–10.16, and *other*: OR 2.97, 95% CI 1.11–7.94), RAP (OR 4.93, 95% CI 2.84–8.58), prior pancreatic interventions (OR 3.10, 95% CI 1.20–8.02), smoking (OR 2.33, 95% CI 1.14–4.78), and male sex (OR 2.06, 95% CI 1.05–4.05) were independently associated with CP.

Conclusion: Disease progression was observed in a quarter of pancreatitis patients. We identified several risk factors that may be helpful to devise personalized strategies with the intention to reduce the impact of disease progression in patients with AP.

INTRODUCTION

Over the years, the incidence of acute pancreatitis (AP) has gradually increased (1, 2). Although most patients fully recover from a first episode of AP, a subset of patients develop recurrent acute pancreatitis (RAP), chronic pancreatitis (CP) or pancreatic cancer (3-5). RAP exposes patients to new episodes of considerable risks of pancreatitis-related complications (5). CP is a debilitating and difficult to manage disease, which has a profound impact on patients' quality of life (QoL) (6, 7). Furthermore, with pancreatic cancer being one of the most fatal malignancies with an overall actual 5-year survival rate below 5% (8), it is crucial to gain insight into which patients are at risk for disease progression as preventive measures and a more intensive follow-up could be offered to these patients.

Several previous cohort studies on transition of AP to RAP and CP have been published (3, 5, 9-12). However, most of these studies originated from a time when AP and CP were seen as separate diseases. To date, evidence suggests that AP, RAP, and CP represent a disease continuum. The mechanisms and risk factors underlying disease progression, however, are still not properly understood (13). Furthermore, these previous studies do not consider the association between AP and pancreatic cancer. AP has previously been linked to pancreatic cancer, but it is still unclear whether there is a direct correlation or if this relationship is solely driven by progression to RAP and CP (14-17). Furthermore, once diagnosed with CP, little is known whether the risk for pancreatic cancer differs for patients with or without a previous diagnosis of RAP.

This long-term follow-up study aims to gain insight into the incidence of and factors associated with transition to RAP, CP, and pancreatic cancer following a first episode of AP.

METHODS

Study design and population

This study is a long-term post-hoc analysis of a prospective nationwide cohort study to investigate the risk of and factors associated with disease progression. Patients were selected from a nationwide cohort of AP patients who were prospectively registered in a consecutive manner between 2008 and 2015. A subset of these patients were included in previous trials of the Dutch Pancreatitis Study Group (DPSG) (18-21). For the present study, only patients with a first episode of AP from 17 different hospitals were eligible for inclusion. AP was defined according to the 2012 revised Atlanta classification (22). An overview of the definitions of the different etiologies is provided in the Supplementary Appendix. Exclusion criteria included no survival of index admission,

(suspected) CP or pancreatic cancer prior to the index date, missing baseline data that could not be retrieved, and loss to follow-up. Written informed consent was obtained from each participant prior to registration. Both the registration cohort study and the previous trials were approved by a central medical ethics committee. All authors had access to the study data and reviewed and approved the final manuscript.

Data collection

Demographic and clinical characteristics at index admission were prospectively collected during the patients' inclusion in the various trials. Medical records were checked for disease progression, readmissions, laboratory and imaging reports, endoscopic or surgical pancreatic interventions, and mortality during long-term follow-up by using a standardized case record form. Additionally, a standard follow-up questionnaire regarding alcohol and smoking behavior (including quit dates in the case of smoking or alcohol cessation), medication use, QoL (i.e., SF-36), and pain severity (i.e., Izbicki Pain Questionnaire) was sent via post to patients who were still alive at the end of follow-up. Non-responders received up to two reminders. Data were checked for completeness and verified by the second author (NS). Any discrepancies were resolved by discussion until consensus was reached.

Study outcomes

The primary endpoints were RAP, CP or pancreatic cancer. RAP was defined as a new episode of AP meeting the revised Atlanta criteria and requiring hospitalization (22). Definite CP was diagnosed according to the M-ANNHEIM-criteria (23). Pancreatic cancer was diagnosed based on histopathology or detected on imaging when no histology was obtained. Secondary endpoints included new onset of diabetes mellitus and/or exocrine pancreatic insufficiency (EPI), medication for (potential) pancreatic pain, endoscopic or surgical pancreatic interventions, QoL, pain severity, and mortality due to pancreatic pathology. EPI was defined in case of a fecal elastase-1 test < 200 µg/g or use of exogenous pancreatic enzymes. Diabetes mellitus was registered when patients were using oral diabetic medication or insulin therapy. The follow-up period was defined as the time between initial enrollment and the date of data collection or the date of death for non-surviving patients.

Data analysis and statistical methods

Data were analyzed by using SPSS version 28 (IBM Corp: Armonk, NY, USA). Categorical data are presented as frequencies with percentages and continuous variables as medians with interquartile ranges (IQR). Between-group differences were analyzed using the Mann-Whitney U test for continuous data, and Fisher's exact test or χ^2-test for categorical data. Logistic regression models were performed to identify potential risk factors for disease progression and presented as odds ratios (ORs) with their respective

95% confidence intervals (CI). A subgroup analysis in biliary pancreatitis patients was performed to evaluate the protective role of cholecystectomy and endoscopic retrograde cholangiopancreatography (ERCP) in preventing RAP. For CP, a subgroup analysis was performed for patients without a history of RAP. In the logistic regression models, missing data were handled by using multiple imputation for variables with less than 20% missing values. Additionally, sensitivity analyses on the original dataset were performed. Cox proportional hazards models were used to calculate the cumulative incidence risk scores for RAP, CP, and pancreatic cancer. Results were stratified by initial etiology and by history of RAP. Furthermore, subgroup analyses were performed for patients in whom preventive measures (i.e., ERCP, cholecystectomy, alcohol- and smoking counselling) were taken as proposed in current guidelines to lower the risk for disease progression. A two-sided p-value of less than 0.05 was considered significant.

RESULTS

Study population

In total, 1,377 patients were prospectively registered of whom 1,184 were included in this long-term follow-up study (Figure S1). Median follow-up was 9 years (IQR 7 – 11). Patient and disease characteristics at baseline are provided in Table 1. The median age was 59 years (IQR 45 – 71) and 56% were male. The most frequent etiology of AP was biliary (63%), followed by alcoholic (13%) and idiopathic (13%). The majority of patients had a mild disease course (70%). In 269 moderately-severe AP patients (23%), AP was complicated by transient organ failure and/or local complications. In total, 82 patients (7%) developed persistent organ failure (i.e., severe pancreatitis). The follow-up questionnaire was sent to 917 patients (77%) of whom 370 responded (response rate: 40%).

Study outcomes

RAP occurred in 301 patients (25%), with a median time from the initial pancreatitis episode of 9 months (IQR 2 – 34) (Table 2). CP was diagnosed in 72 patients (6%) after a median follow-up period of 31 months (IQR 7 – 61) and was preceded by RAP in 45 patients (63%). Pancreatic cancer was diagnosed in 14 patients (1%) of whom one patient was previously diagnosed with both RAP and CP and five patients with only RAP. Median time to pancreatic cancer diagnosis was 24 months (IQR 4 – 84). New onset diabetes and EPI was observed in 12% (n=147) and 9% (n=105) of patients, respectively. Pancreatic surgery was performed in 37 patients (3%), 60 patients underwent endoscopic pancreatic therapy (5%) and 52 patients (4%) needed medical treatment for pancreatic pain. Overall, 267 patients (23%) died during follow-up. Death was related to pancreatic diseases in 31 patients (3%).

Table 1. Patient and disease characteristics in 1,184 patients with a first episode of acute pancreatitis

	n		
Age (year), median (P25 – P75)	1184	59 (45 – 71)	
Male sex, no. (%)	1184	660 (56)	
Body mass index, median (P25 – P75)	741	28 (25 – 31)	
Etiology, no. (%)	1184		
Biliary		740 (63)	
Alcoholic		156 (13)	
Idiopathic		156 (13)	
Other		132 (11)	
Smoking, no. (%)	1029		
Current		276 (23)	
Past		151 (13)	
Never		602 (51)	
Alcohol, no. (%)	1066		
Current*		649 (55)	
Heavy users		112 (10)	
Excessive users		49 (4)	
Social users		488 (41)	
Past		35 (3)	
Never		382 (32)	
ASA-classification, no. (%)	1184		
I		225 (19)	
II		520 (44)	
III		430 (36)	
IV		9 (1)	
C-Reactive Protein (CRP) < 48 hours after admission, median (P25 – P75)	1176	162 (73 – 287)	
Leukocytes < 48 hours after admission, median (P25 – P75)	1178	15 (11 – 19)	
APACHE-score < 48 hours after admission, median (P25 – P75)	1172	7 (4 – 9)	
IMRIE score < 48 hours after admission, median (P25 – P75)	1173	1 (1 – 2)	
Severity according to Atlanta, no. (%)		Mild	Moderate/severe
Predicted severity at admission#	1175	506 (43)	669 (57)
Actual severity after admission	1184	833 (70)	269 (23) / 82 (7)
CT Severity Index score, median (P25 – P75)+	215	6 (4 – 8)	
Necrosis, no. (%)+	351	257 (22)	
Extent necrosis, no. (%)+	253		
Pancreatic parenchymal		33 (3)	
Peripancreatic tissue		80 (7)	

Table 1. Patient and disease characteristics in 1,184 patients with a first episode of acute pancreatitis (*continued*)

Both		140 (12)
Peripancreatic collections, no. (%)+	351	305 (26)
Persistent organ failure, no. (%)	1184	82 (7)
Pancreatic intervention, no. (%)	1184	119 (10)
Radiological percutaneous drainage		83 (7)
Endoscopic procedure†		64 (5)
Surgical procedure‡		37 (3)
ERCP < 3 months after onset acute pancreatitis, no. (%)**	1182	263 (22)
Cholecystectomy, no. (%)	1182	689 (58)
Prior to first episode of acute pancreatitis		105 (9)
Performed after first episode of acute pancreatitis		584 (49)
< 3 months after onset acute pancreatitis		400 (34)
> 3 months after onset acute pancreatitis		182 (15)
Date unknown		2 (2)
Follow-up questionnaire, no. (%)	1184	
Questionnaire completed		370
Questionnaire not completed		547
No reply		414
Current address unknown		48
Refused questionnaire		85
Not available for questionnaire (i.e., no survival)		267 (23)

**Divided into categories as defined by the National Institute for Public Health and Environment: Heavy users = at least once a week ≥ 4 units/day (women)/ ≥ 6 units/day (men), excessive users = > 21 units/week (men)/>14 units/week (woman). #Predicted severe acute pancreatitis was defined as an Acute Physiology and Chronic Health Evaluation (APACHE II) score ≥ 8, Imrie score ≥ 3 or C-reactive protein > 150 mg/L. +Only described for the moderately severe and severe acute pancreatitis patients (n = 351). †Endoscopic drainage and/or endoscopic necrosectomy. ‡Surgical drainage and/or surgical necrosectomy. **Only ERCP procedures that included a sphincterotomy, nettoyage/stone-extraction and/or stenting therapy were included in the evaluation. Abbreviations: ASA American Society of Anesthesiologists, ERCP endoscopic retrograde cholangiopancreatography.*

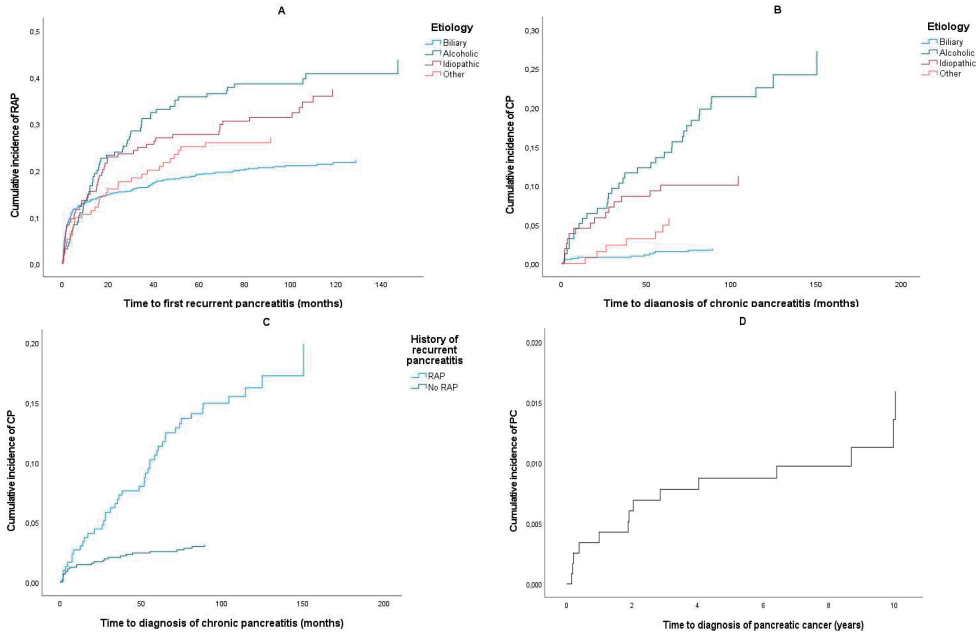
Table 2. Primary and secondary study endpoints of 1,184 patients with a first episode of acute pancreatitis

	n	
Follow up duration (years), median (P25 – P75)	1184	9 (7 – 11)
Mortality, no. (%)	1184	267 (23)
Due to pancreatic diseases	241	31 (3)
Recurrent pancreatitis	1184	301 (25)
Number of recurrences	301	
1 episode		179 (15)
2 episodes		49 (4)
≥3 episodes		73 (6)
Time to recurrent pancreatitis (months), median (P25 – P75)	301	9 (2 – 34)
Etiology first acute pancreatitis episode, no. (%)	301	
Biliary		153/740 (21)
Alcoholic		62/156 (40)
Idiopathic		52/156 (33)
Other		34/132 (26)
Chronic pancreatitis, no. (%)	1184	72 (6)
Time to chronic pancreatitis (months), median (P25 – P75)	71	31 (7 – 61)
Etiology first acute pancreatitis, no. (%)	72	
Biliary		13/740 (2)
Alcoholic		35/156 (22)
Idiopathic		16/156 (10)
Other		8/132 (6)
History of recurrent pancreatitis	72	45/72 (63)
Pancreatic cancer, no. (%)	1183	14 (1)
Time to pancreatic cancer (months), median (P25 – P75)	14	24 (4 – 84)
Etiology first acute pancreatitis, no. (%)	14	
Biliary		3/740 (0)
Alcoholic		2/156 (1)
Idiopathic		7/155 (5)
Other		2/132 (2)
History of recurrent pancreatitis	14	5/14 (36)
History of chronic pancreatitis	14	0/14 (0)
History of recurrent and chronic pancreatitis	14	1/14 (7)
New onset diabetes, no. (%)	1184	147 (12)
Exocrine pancreatic insufficiency, no. (%)	1184	105 (9)
Medication for pancreatic pain, no. (%)	1181	52 (4)
Endoscopic therapy during follow-up, no. (%)	1184	60 (5)
Surgery during follow-up, no. (%)	1183	37 (3)
Pancreatic resection		26 (2)
Other surgical procedures*		13 (1)

**Surgical drainage (n = 3), surgical necrosectomy (n = 2), bypass surgery because of duodenal obstruction (n =6) and fistulotomy (n = 2).*

Recurrent acute pancreatitis

The risks of RAP for different variables after multiple imputations are summarized in Table 3 (see Table S1 for non-imputed data). In the multivariate model, factors independently associated with development of RAP were alcoholic and idiopathic pancreatitis (OR 2.70, 95% CI 1.51 – 4.82 and OR 2.06, 95% CI 1.40 – 3.02), and no pancreatic intervention(s) performed during the initial episode (OR 1.82, 95% CI 1.10 – 3.01). In the subgroup analysis for biliary pancreatitis patients, independent protective factors for RAP were ERCP ≤ 3 months after onset of AP (OR 0.37, 95% CI 0.23 – 0.61) and cholecystectomy when performed prior to or ≤ 3 months after onset of AP (OR 0.16, 95% CI 0.11 – 0.25) (Table S2). The cumulative risk for RAP over 9 years was the highest among patients with an initial alcoholic etiology (40%) (Figure 1A).



Cumulative incidence for (A) recurrent acute pancreatitis, (B) chronic pancreatitis when stratified by etiology, (C) chronic pancreatitis when stratified by history of recurrent acute pancreatitis and (D) for pancreatic cancer.

Figure 1. Cumulative incidence over time for disease progression.

Table 3. Factors associated with recurrent acute pancreatitis – univariate and multivariate analyses

		Univariate analyses		Multivariate analyses	
Variable	**n/N (%)**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Age (years)		1.00 (.99 – 1.00)	.341		
Gender					
Male	178/660 (27%)	1.20 (.92 – 1.57)	.170		
Female	123/524 (23%)	1			
BMI*		.97 (.94 – 1.00)	.074		
Etiology					
Biliary	153/740 (21%)	1		1	
Alcoholic	62/156 (40%)	2.53 (1.75 – 3.65)	<.001	2.70 (1.51 – 4.82)	<.001
Idiopathic	52/156 (33%)	1.92 (1.32 – 2.80)	.001	2.06 (1.40 – 3.02)	<.001
Other	34/132 (26%)	1.33 (.87 – 2.04)	.191	1.40 (.90 – 2.17)	.134
Smoking					
Current	93/316 (29%)	1.46 (1.03 – 2.05)	.032	1.12 (.75 – 1.70)	.581
Past	52/173 (30%)	1.48 (.99 – 2.20)	.055	1.39 (.92 – 2.11)	.122
Never	156/695 (22%)	1		1	
Alcohol					
Heavy users	39/114 (34%)	1.57 (1.00 – 2.47)	.048	.71 (.36 – 1.40)	.317
Excessive users	22/64 (34%)	1.60 (.66 – 3.90)	.280	.97 (.41 – 2.30)	.939
Social users	123/536 (23%)	.90 (.65 – 1.25)	.532	.81 (.58 – 1.14)	.231
Past	10/40 (25%)	1.08 (.48 – 2.43)	.849	.92 (.41 – 2.10)	.848
Never	107/430 (25%)	1		1	
ASA-classification					
I	47/225 (21%)	1		1	
II	123/520 (24%)	1.17 (.80 – 1.72)	.409	1.05 (.71 – 1.57)	.793

III	128/430 (30%)	1.61 (1.10 – 2.35)	.015	1.22 (.80 – 1.84)	.358
IV	3/9 (33%)	1.89 (.46– 7.86)	.379	1.72 (.40 – 7.33)	.466
CRP < 48 hours after admission		1.00 (1.00 – 1.00)	.740		
Leukocytes < 48 hours after admission		1.00 (.99 – 1.02)	.919		
APACHE II score		.98 (.94 – 1.01)	.179		
Modified Glasgow score		.90 (.81 – 1.01)	.062		
Severity according to Atlanta					
Mild	91/351 (26%)	1.04 (.78 – 1.38)	.796		
Moderate/severe	210/833 (25%)	1			
Pancreatic necrosis					
Yes	44/177 (25%)	.97 (.67 – 1.41)	.862		
No	257/1007 (26%)	1			
Acute (peripancreatic) fluid collection(s)					
Yes	74/309 (24%)	.90 (.66 – 1.22)	.503		
No	227/875 (26%)	1			
Local complications[a]					
Yes	82/332 (25%)	.95 (.71 – 1.28)	.734		
No	219/852 (26%)	1			
Persistent organ failure					
Yes	17/82 (21%)	.75 (.43 – 1.31)	.313		
No	284/1102 (26%)	1			
Pancreatic intervention(s) during first episode					
Yes	21/119 (18%)	.60 (.37 – .98)	.042	.55 (.33 – .91)	.020
No	280/1065 (26%)	1		1	
Follow-up (years)		1.04 (1.00 – 1.09)	.059		

**BMI not imputed as data were only available in 741 patients. aLocal complications: parenchymal necrosis, peripancreatic necrosis and/or acute (peripancreatic) fluid collection(s).*

Table 4. Factors associated with chronic pancreatitis – univariate and multivariate analyses

	Univariate analyses			Multivariate analyses with RAP as covariate		Multivariate analyses without RAP as covariate	
Variable	**n/N (%)**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Age (years)		.98 (.96 – .99)	<.001	.99 (.97 – 1.01)	.378	.99 (.97 – 1.01)	.167
Gender							
Male	58/660 (8%)	3.51 (1.94 – 6.37)	<.001	2.06 (1.05 – 4.05)	.035	1.98 (1.02 – 3.83)	.044
Female	14/524 (3%)	1		1		1	
BMI*		.86 (.80 – .92)	<.001				
Etiology							
Biliary	13/740 (2%)	1		1		1	
Alcoholic	35/156 (22%)	16.18 (8.32 – 31.46)	<.001	5.24 (1.94 – 14.16)	.001	6.51 (2.47 – 17.22)	<.001
Idiopathic	16/156 (10%)	6.39 (3.01 – 13.58)	<.001	4.57 (2.05 – 10.16)	<.001	5.53 (2.53 – 12.10)	<.001
Other	8/132 (6%)	3.61 (1.47 – 8.88)	.005	2.97 (1.11 – 7.94)	.030	3.06 (1.18 – 7.98)	.022
Smoking							
Current	41/316 (13%)	5.02 (2.83 – 8.88)	<.001	2.33 (1.14 – 4.78)	.021	2.29 (1.17 – 4.48)	.016
Past	11/173 (6%)	2.34 (1.09 – 5.03)	.030	1.96 (.84 – 4.61)	.122	1.93 (.83 – 4.49)	.125
Never	20/695 (3%)	1		1		1	
Alcohol							
Heavy users	22/114 (19%)	11.74 (5.11 – 26.96)	<.001	2.19 (.67 – 7.10)	.193	1.95 (.62 – 6.11)	.251
Excessive users	10/64 (16%)	9.43 (3.24 – 27.42)	<.001	3.12 (.90 – 10.86)	.074	2.91 (.85 – 9.98)	.088
Social users	28/536 (5%)	2.73 (1.23 – 6.05)	.014	1.76 (.75 – 4.14)	.195	1.69 (.72 – 3.95)	.227
Past	3/40 (8%)	4.03 (1.02 – 15.90)	.046	2.33 (.50 – 10.98)	.284	2.80 (.63 – 12.35)	.175
Never	9/430 (2%)	1		1		1	
ASA-classification							
I	10/225 (4%)	1		1		1	
II	22/520 (4%)	.95 (.44 – 2.04)	.895	.71 (.29 – 1.74)	.450	.76 (.32 – 1.83)	.544
III	40/430 (9%)	2.21 (1.08 – 4.50)	.030	.79 (.29 – 2.13)	.644	.88 (.33 – 2.30)	.786

IV	0/9 (0%)	.00 (.00 –)	.999	.00 (.00 –)	.999	.00 (.00 –)	.999
CRP < 48 hours after admission		1.00 (1.00 – 1.00)	.038	1.00 (1.00 – 1.00)	.786	1.00 (1.00 – 1.00)	.792
Leukocytes < 48 hours after admission		1.01 (.99 – 1.03)	.433				
APACHE II score		.99 (.92 – 1.05)	.661				
Modified Glasgow score		.91 (.74 – 1.11)	.336				
Severity according to Atlanta							
Mild	45/833 (5%)	1					
Moderate/severe	27/351 (8%)	1.46 (.89 – 2.39)	.134				
Pancreatic necrosis							
Yes	17/177 (10%)	1.84 (1.04 – 3.26)	.036	.88 (.36 – 2.19)	.788	1.07 (.44 – 2.62)	.882
No	55/1007 (5%)	1		1		1	
Acute (peri-)pancreatic fluid collection(s)							
Yes	26/309 (8%)	1.66 (1.01 – 2.74)	.048	1.10 (.51 – 2.37)	.802	.96 (.46 – 2.01)	.905
No	46/875 (5%)	1		1		1	
Local complications[a]							
Yes	26/332 (8%)	1.49 (.91 – 2.46)	.117				
No	46/852 (5%)	1					
Persistent organ failure							
Yes	6/82 (7%)	1.24 (.52 – 2.95)	.628				
No	66/1102 (6%)	1					
Pancreatic intervention during first episode							
Yes	14/119 (12%)	2.32 (1.25 – 4.29)	.008	3.10 (1.20 – 8.02)	.020	2.13 (.85 – 5.33)	.108
No	58/1065 (5%)	1		1		1	
Recurrent acute pancreatitis						*Not included*	
Yes	45/301 (15%)	5.57 (3.39 – 9.16)	<.001	4.93 (2.84 – 8.58)	<.001		
No	27/883 (3%)	1		1			
Follow-up (years)		1.06 (.98 – 1.16)	.143				

**BMI not imputed as data were only available in 741 patients. aLocal complications: parenchymal necrosis, peripancreatic necrosis and/or acute (peripancreatic) fluid collection(s).*

Subgroup analyses for biliary interventions, smoking and alcohol

An overview of the preventive measures taken in our biliary cohort and the recurrence rate is provided in the Supplementary Appendix (Figure 2A and 2B). ERCP ≤ 3 months after hospitalization was performed in 233 patients (31%). In these patients, 10% (24/233) developed RAP after ERCP. The overall recurrence rate within this subgroup was 15% (36/233). This was significantly lower compared to patients who underwent an ERCP > 3 months after AP (P<.001), but not significantly different from those in whom no ERCP was performed (P=.287). Cholecystectomy was performed before or ≤ 3 months after the first episode of AP in 61% of biliary patients (n=446). The lowest recurrence rate (14%) was observed in this subgroup. Cholecystectomy > 3 months after hospitalization was not associated with a lower recurrence rate compared to no cholecystectomy. No significant differences in recurrence rates were observed between patients who quit smoking versus continued smoking (Table S4) and between patients who stopped drinking alcohol versus continued drinking (Table S5A). Within the subgroup of alcoholic pancreatitis patients, alcohol cessation was significantly associated with a lower recurrence rate compared with long-term alcohol consumption (p=.043) (Table S5B).

Chronic pancreatitis

Table 4 presents the results of the logistic regression analyses for development of CP (see Table S6 for non-imputed data). In multivariate analysis, non-biliary etiology (*alcohol*: OR 5.24, 95% CI 1.94 – 14.16, *idiopathic*: OR 4.57, 95% CI 2.05 – 10.16, and *other*: OR 2.97, 95% CI 1.11 – 7.94), RAP (OR 4.93, 95% CI 2.84 – 8.58), pancreatic intervention(s) performed during the initial episode (OR 3.10, 95% CI 1.20 – 8.02), smoking (OR 2.33, 95% CI 1.14 – 4.78), and male sex (OR 2.06, 95% CI 1.05 – 4.05) were independently associated with CP. Multivariate analyses with RAP removed as covariate are presented in Table 4. Patients with alcoholic AP (22%) and a history of RAP (15%) had the highest cumulative risk for developing CP over 9 years (Figure 1B and 1C).

Subgroup analyses for smoking and alcohol

No significant differences in progression rates to CP were observed between patients who continued smoking and drinking versus patients who reported cessation of smoking and alcohol cessation at long-term follow-up (Table S7 and S8).

Pancreatic cancer

The number of patients who developed pancreatic cancer was insufficient to perform multivariate analysis. Of the 14 patients who developed pancreatic cancer, 7 were diagnosed within 2 years after onset of AP. In 57% of these patients (4/7) the cause of the initial AP episode was unknown. When introducing a 5-years lag period, 5 patients

remained of whom 1 patient with idiopathic AP. Pancreatic cancer was preceded by RAP in 6 patients (43%) of whom 1 patient was also diagnosed with CP (Figure 1D).

Quality of life and pain severity

QoL was not significantly different between patient with and without progression to RAP and CP (p>.05) (Table S9). Regarding pain severity, both RAP and CP patients reported significantly higher Izbicki Pain scores (P=.004 and p<.001) compared to their controls.

DISCUSSION

This long-term clinical follow-up study showed that 25% of patients developed RAP, 6% of patients progressed to CP, and 1% of patients were diagnosed with pancreatic cancer. Median duration from index admission to RAP, CP, and pancreatic cancer was 9 months (IQR 2 – 34), 31 months (IQR 7 – 61), and 24 months (IQR 4–84), respectively. Several independent predictive factors were identified for both RAP and CP.

The reported progression rates after a first episode of AP vary widely among previous studies (3, 5, 9-12). The latest meta-analysis, with a median follow-up between 18-180 months, reported a pooled prevalence rate of 22% for RAP and 10% for CP (24). Some of the included studies were population-based matched cohort studies, which allow for a smaller sample size and automatically control for confounding factors by socioeconomic position (14, 15). A drawback of these studies is that the effects of matching factors on disease occurrences of interest (i.e., RAP, CP, and pancreatic cancer) could not be evaluated. Moreover, no adjustment were made for potentially confounding factors such as alcohol and smoking due to the limited data available. Therefore, the incidence of and risk factors associated with transition to these pancreatic diseases following a first episode of AP are best investigated in prospective observational cohort studies. The risk of progression after a first episode of AP has been investigated by our study group in such manner before (3, 4). In this previous study, 17% and 8% of patients developed RAP and CP, respectively (3). Pancreatic cancer following AP was observed in 1% of patients (4). In both previous studies, however, patients were followed up for a maximum of 5 years, which is probably too short and may have led to an underestimation of the progression rate. In the present study with a significantly longer follow-up period, 25% of patients were diagnosed with RAP of whom 33 patients (11%) developed the first recurrent attack after more than 5 years follow-up. This leaves us with a recurrence rate of 23% within 5 years, which is higher than our previous study, but comparable to the meta-analysis (24). On the contrary,

we found a lower incidence of CP, which can be explained by a smaller proportion of alcoholic pancreatitis patients included in the current study (25). Furthermore, our incidence rate of pancreatic cancer was comparable to the previous study (4), but significantly higher compared to the 0.2% incidence rate of the Dutch general population between 2008 and 2011 (26). When introducing a lag-period of 2 and 5 years, as proposed by previous studies to avoid misdiagnosis of pancreatic cancer as AP (14, 27), our incidence rate was still three and two times higher (0.6% and 0.4%, respectively). In our study, 50% of the pancreatic cancer patients (n=7) were diagnosed within 2 years after the first pancreatic episode, of whom 4 were idiopathic pancreatitis patients, indicating a possible diagnostic delay. This may raise the question whether follow-up imaging would allow for an earlier diagnosis in idiopathic pancreatitis patients. As follow-up imaging has previously been proposed for these patients to further investigate etiology and identify the need of a cholecystectomy, screening for pancreatic cancer may be another indication (28, 29).

Several important findings emerged from our data when examining risk factors for disease transition. Consistent with other studies, the highest cumulative incidence of RAP and CP was observed among alcoholic pancreatitis patients (10, 11). Alcoholic pancreatitis was an independent risk factor for both RAP and CP, which resulted in a three- and five-times higher risk compared with biliary pancreatitis. Independent preventive factors for RAP in biliary patients were an ERCP and cholecystectomy prior to or ≤ 3 months after onset of AP. As shown in other studies (30, 31), our results emphasize once again the importance of these preventive measures. Although these interventions are already standard of practice for biliary pancreatitis, the timing of an ERCP and cholecystectomy can be challenging, especially in severe AP patients. With respect to ERCP, a conservative treatment strategy is opted for patients without cholangitis or persistent choledocholithiasis. However, in the case of patients who are considered unfit for surgery, an ERCP with sphincterotomy should be considered to reduce the risk of recurrent biliary events (30). In patients fit for surgery, a cholecystectomy should preferably be performed during index admission in mild pancreatitis patients, and within 8 weeks in severe pancreatitis patients in the absence of peripancreatic collections (32). In our cohort of biliary patients, no significant difference in recurrence rate was observed between patients who underwent ERCP within 3 months after AP and patients in whom ERCP was not performed. However, confounding by indication may have played a role, as ERCP is only indicated in cases of proven choledocholithiasis. In the long-term, not all of these patients need to undergo ERCP. However, in case of choledocholithiasis, our results show that ERCP should preferably be performed < 3 months after hospitalization. For cholecystectomy, the protective effect is negligible compared to no cholecystectomy if performed > 3 months after the onset of AP. Therefore, to significantly reduce the risk of recurrent gallstone-related

complications, cholecystectomy should ideally be performed in all patients with biliary pancreatitis within 3 months after the first episode of AP. Our study shows that there is significant room for improvement in the follow-up of patients with biliary pancreatitis, as cholecystectomy was not performed in one quarter of the patients. Furthermore, we have demonstrated that patients with biliary pancreatitis have the lowest risk of developing CP if the causative factor is appropriately treated.

Interestingly, the risk of RAP was lower in patients who underwent pancreatic interventions during the index episode, but at the expense of a higher risk of developing CP. A possible explanation for this latter being that pancreatic interventions might be prone for causing permanent pancreatic damage and consequently accelerating chronic inflammation. Confounding by indication could also play a role here as pancreatic interventions are more frequently performed in patients with moderate/severe pancreatitis, in our population, however, disease severity and complications proved not to be associated with disease progression. Furthermore, a recent study showed that one in four necrotizing pancreatitis patients suffer from a disconnected pancreatic duct, which is associated with higher risk of RAP if not treated accordingly (33). This partly explains the higher risk of RAP for patients not undergoing endoscopic drainage with long-term indwelling of double-pigtail plastic stents. Previous studies on factors associated with disease progression yielded conflicting results for pancreatic necrosis and disease severity (3, 8, 24). In this study, disease severity and complications were no determinants of disease progression, which is consistent with the most-recent meta-analysis (24). To further explore the impact of pancreatic necrosis on progression rate, we have performed additional regression analyses for disease severity and complications within the subgroup of patients with predicted severe pancreatitis, which failed to detect any relevant statistically differences [data not shown]. For CP, other independent risk factors than those previously mentioned, were male sex, smoking, and RAP, which is in line with previous studies (3, 25). In the majority of patients, CP was preceded by RAP (63%). Post-hoc risk analyses for the impact of lifestyle modifications showed that alcohol cessation significantly reduced the risk of RAP in patients with alcoholic pancreatitis, which was not the case for CP. Associations between smoking cessation and a reduced risk of RAP and CP were also not found. This was presumably due to limited data available on current smoking and alcohol use. Their impact on disease progression may therefore be underestimated. Both smoking and alcohol have, however, previously been identified as important independent risk factors for disease progression and related complications. Therefore, counselling for alcohol and smoking cessation should be standard of follow-up care (34-37). In our study population, disease progression was not significantly associated with a lower QoL.

This study evaluated the likelihood of developing pancreatic diseases following AP after a median follow up of more than 9 years in a prospective cohort of 1,184 patients and therefore provides a more in-depth insight compared to previous studies. Additionally, our study suggests that preventive measures for disease progression are not sufficiently implemented in current practice, which should become a point of attention in future care.

This study has some limitations. First, follow-up data were retrospectively collected, which may have led to information bias. Second, data on current smoking and alcohol consumption were only provided by a limited number of patients. Third, our ability to explore the relation between CP and pancreatic cancer was limited due to a small subset of CP patients (37). Finally, we have pragmatically chosen a cut-off of 3 months between the first presentation of acute biliary pancreatitis and the performance of biliary procedures, as logistics (i.e., waiting lists) often delay these procedures. Although we acknowledge that this is longer than the recommendations based on the existing literature, we believe that the use of this interval more accurately reflects current clinical practice (38).

CONCLUSION

One in four patients with AP will develop RAP, CP, or pancreatic cancer after a first episode of AP. We identified several risk factors that may be helpful to devise personalized strategies, such as lifestyle counselling, biliary interventions or more intense follow-up for those at risk for disease progression. Our findings should encourage physicians to improve preventive interventions and follow-up care for those patients at risk for pancreatic disease progression.

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Supplementary file S1. Diagnostic criteria for the different etiologies

Alcoholic etiology
>3 units/day or >4 units 48hrs prior to the start of acute pancreatitis, in absence of gallstones and/or CBD dilatation

Biliary etiology
In the case of one of the following criteria
1. Gallstones and/or sludge diagnosed on imaging (transabdominal or endoscopic ultrasound or computed tomography);
2. A dilated common bile duct on ultrasound (>8 mm in patients ≤75 years old or >10 mm in patients >75 years old);
3. Alanine aminotransferase (ALAT) level >2 times higher than normal values

And in the absence of alcohol abuse or evidence of other etiology (high risk medication/genetic factors etc.)

Hypertriglyceridemia as etiology
Fasting serum triglyceride >1000 mg/dl (11.2 mmol/l), in absence of criteria for a biliary etiology

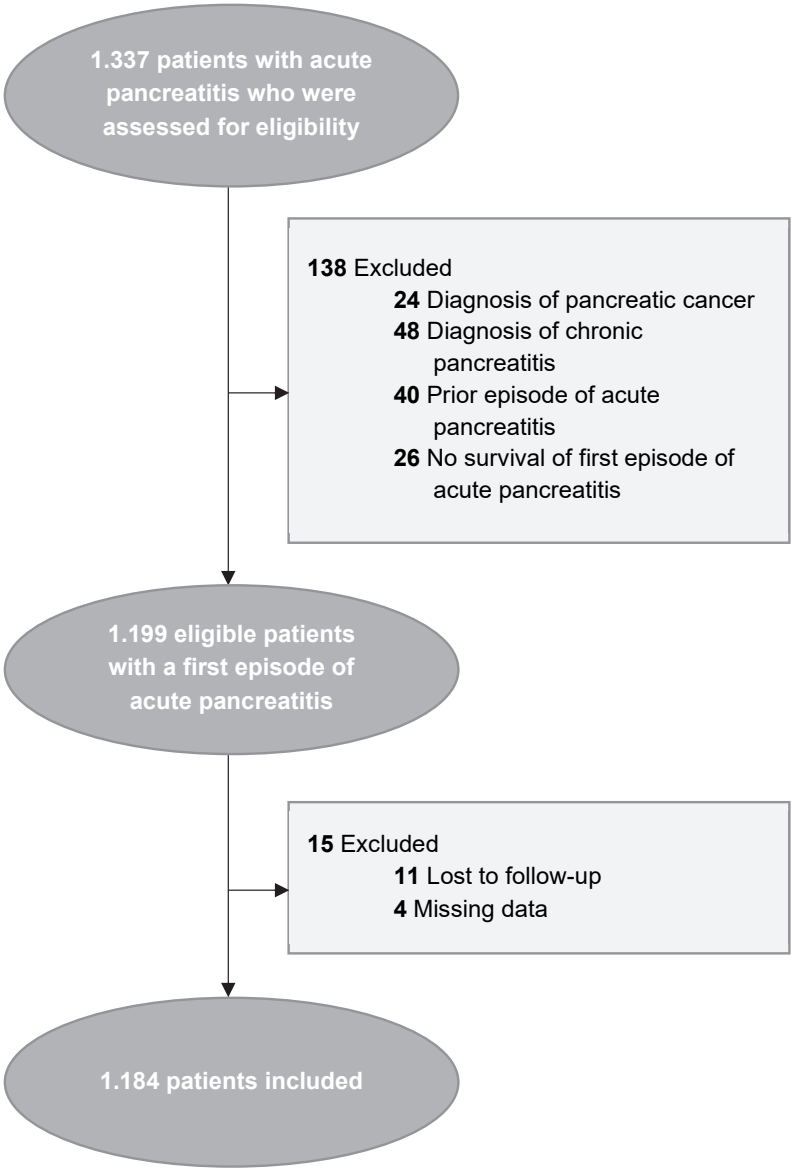
Hypercalcemia as etiology
Serum calcium >12 mg/dl or 3 mmol/l, in absence of criteria for a biliary etiology

Post-ERCP as etiology (Coton criteria, 4 of 4)
(1) Upper abdominal pain;
(2) Serum lipase or amylase levels above three times the upper level of normal;
(3) Timeframe: 24hrs after ERCP
(4) At least 2 days of hospitalization after ERCP

Medication as etiology
Use of 1 or more drugs with a known association with AP, in absence of criteria for a biliary etiology. Definite association: Acetaminophen, asparaginase, azathioprine, bortezomib, capecitabine, carbamazepine, cimetidine, cisplatin, cytarabine, didanosine, enalapril, erythromycin, oestrogens, furosemide, hydrochlorothiazide, i erferon alfa, itraconazole, lamivudine, mercaptopurine, mesalazine, olsalazine, methyldopa, metronidazole, octreotide, olanzapine, opiates, oxyphenbutazone, pentamidine, pentavalent antimony compounds, phenformin, simvastatin, steroids, sulfasalazine, co-trimoxazole

Idiopathic etiology

Patients lacking any of the above-mentioned criteria and with no recent history of surgery/abdominal trauma of any evidence of familial/genetic cause of pancreatitis were classified as idiopathic



Supplementary figure S1. Flowchart patient inclusion

Supplementary table S1. Factors associated with recurrent acute pancreatitis – univariate and multivariate analyses (original dataset)

			Univariate analyses		Multivariate analyses (n = 1009)	
Variable	**N**	**n/N (%)**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Age (years)	1184		1.00 (.99 – 1.00)	.341		
Gender	1184					
Male		178/660 (27%)	1.20 (.92 – 1.57)	.170		
Female		123/524 (23%)	1			
BMI*	741		.97 (.94 – 1.00)	.074		
Etiology	1184			<.001		<.001
Biliary		153/740 (21%)	1		1	
Alcoholic		62/156 (40%)	2.53 (1.75 – 3.65)	<.001	2.50 (1.38 – 4.54)	.003
Idiopathic		52/156 (33%)	1.92 (1.32 – 2.80)	.001	2.23 (1.48 – 3.36)	<.001
Other		34/132 (26%)	1.33 (.87 – 2.04)	.191	1.71 (1.08 – 2.70)	.022
Smoking	1029			.018		.284
Current		87/276 (32%)	1.53 (1.12 – 2.11)	.008	1.20 (.84 – 1.72)	.312
Past		45/151 (30%)	1.41 (.95 – 2.10)	.087	1.37 (.90 – 2.09)	.142
Never		139/602 (23%)	1		1	
Alcohol	1066			.018		.550
Heavy users		39/112 (35%)	1.51 (.96 – 2.37)	.075	.76 (.39 – 1.50)	.432
Excessive users		21/49 (43%)	2.12 (1.15 – 3.89)	.016	1.08 (.50 – 2.31)	.853
Social users		117/488 (24%)	.89 (.65 – 1.21)	.456	.79 (.57 – 1.09)	.151
Past		10/35 (29%)	1.13 (.52 – 2.43)	.759	1.04 (.47 – 2.32)	.918
Never		100/382 (26%)	1		1	
ASA-classification	1184			.050		.962
I		47/225 (21%)	1		1	

II		123/520 (24%)	1.17 (.80 – 1.72)	.409	.97 (.64 – 1.47)	.881
III		128/430 (30%)	1.61 (1.10 – 2.35)	.015	1.06 (.68 – 1.66)	.788
IV		3/9 (33%)	1.89 (.46– 7.86)	.379	1.07 (.19 – 5.88)	.942
CRP < 48 hours after admission	1176		1.00 (1.00 – 1.00)	.653		
Leukocytes < 48 hours after admission	1178		1.00 (.99 – 1.02)	.867		
APACHE II score	1172		.98 (.94 – 1.01)	.227		
Modified Glasgow score	1173		.91 (.82 – 1.01)	.088		
Severity according to Atlanta	1184					
Mild		91/351 (26%)	1.04 (.78 – 1.38)	.796		
Moderate/severe		210/833 (25%)	1			
Pancreatic necrosis	1174					
Yes		44/173 (25%)	.99 (.69 – 1.44)	.969		
No		256/1001 (26%)	1			
Acute (peripancreatic) fluid collection(s)	1176					
Yes		74/305 (24%)	.91 (.67 – 1.23)	.535		
No		227/871 (26%)	1			
Local complications[a]	1176					
Yes		82/326 (25%)	.97 (.72 – 1.30)	.830		
No		219/850 (26%)	1			
Persistent organ failure	1184					
Yes		17/82 (21%)	.75 (.43 – 1.31)	.313		
No		284/1102 (26%)	1			
Pancreatic intervention(s) during first episode	1184					
Yes		21/119 (18%)	.60 (.37 – .98)	.042	.52 (.31 – .89)	.017
No		280/1065 (26%)	1		1	
Follow-up (years)	1184		1.04 (1.00 – 1.09)	.059		

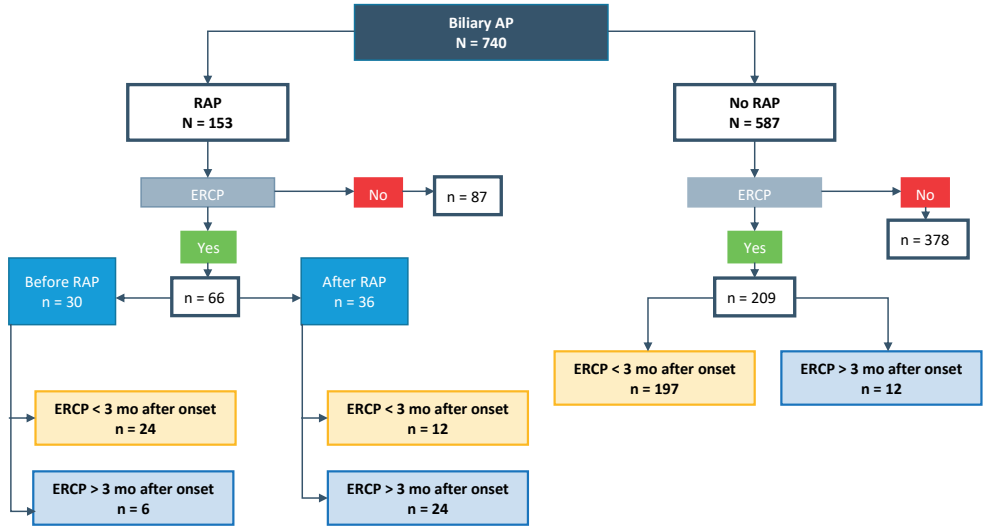
aLocal complications: parenchymal necrosis, peripancreatic necrosis and/or acute (peripancreatic) fluid collection(s).

Supplementary table S2. Factors associated with recurrent acute pancreatitis in biliary pancreatitis patients – univariate and multivariate analyses (imputed dataset)

		Univariate analyses			Multivariate analyses (n = 740)	
Variable	**N**	**n/N (%)**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Age (years)	740		1.01 (1.00 – 1.02)	.220		
Gender	740					
Male		77/367 (21%)	1.04 (.73 – 1.48)	.839		
Female		76/373 (20%)	1			
BMI	479		.99 (.95 – 1.03)	.693		
Smoking	740					
Current		28/137 (20%)	1.09 (.62 – 1.93)	.758	1.06 (.58 – 1.91)	.854
Past		34/113 (30%)	1.83 (1.11– 3.03)	.018	1.63 (.94 – 2.82)	.083
Never		92/490 (19%)	1		1	
Alcohol	740					
Heavy users		2/13 (15%)	.58 (.12 – 2.71)	.486		
Excessive users		8/28 (29%)	1.47 (.25 – 8.57)	.633		
Social users		65/355 (18%)	.73 (.47 – 1.12)	.149		
Past		5/31 (16%)	.64 (.23 – 1.78)	.389	.	
Never		73/313 (23%)	1			
ASA-classification	740					
I		33/173 (19%)	1			
II		60/333 (18%)	.93 (.58 – 1.49)	.771		
III		57/228 (25%)	1.41 (.87 – 2.29)	.160		
IV		3/6 (50%)	4.24 (.82– 21.97)	.085		
CRP < 48 hours after admission	740		1.00 (1.00 – 1.00)	.613		
Leukocytes < 48 hours after admission	740		1.00 (.99 – 1.02)	.683		
APACHE II score	740		1.01 (.96 – 1.05)	.794		

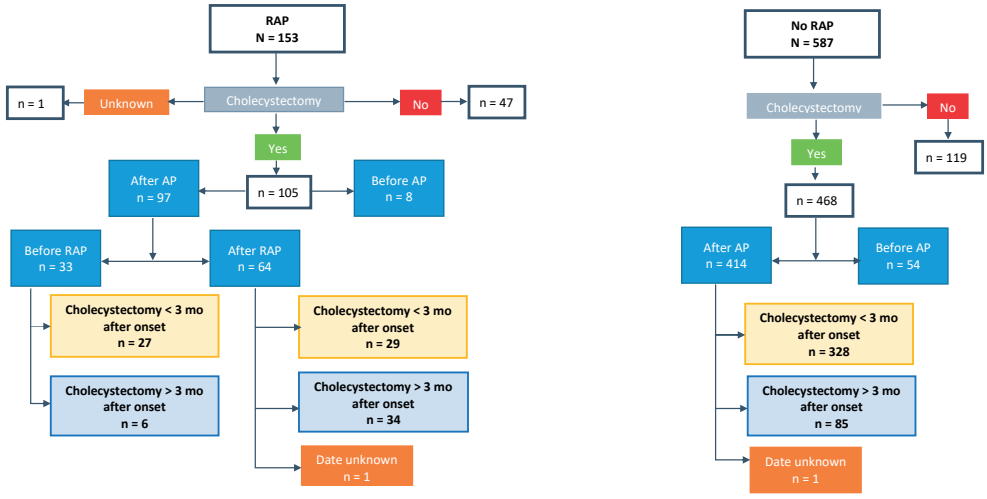
Modified Glasgow score	740		1.01 (.87 – 1.16)	.926		
Severity according to Atlanta	740					
Mild		116/574 (20%)	.88 (.58 – 1.34)	.560		
Moderate/severe		37/166 (22%)	1			
Pancreatic necrosis	740					
Yes		16/84 (19%)	.89 (.50 – 1.60)	.694		
No		137/656 (21%)	1			
Acute (peripancreatic) fluid collection(s)	740					
Yes		28/142 (20%)	.93 (.59 – 1.48)	.771		
No		125/598 (21%)	1			
Local complications[a]	740					
Yes		31/152 (20%)	.98 (.63 – 1.53)	.939		
No		122/588 (21%)	1			
Persistent organ failure	740					
Yes		8/38 (21%)	1.02 (.46 – 2.28)	.953		
No		145/702 (21%)	1			
Pancreatic intervention(s) during first episode	740					
Yes		11/53 (21%)	1.01 (.51 – 2.00)	.988		
No		142/687 (21%)	1			
ERCP ≤ 3 months after onset AP (and before RAP)	740					
Yes		24/221 (11%)	.37 (.23 – .59)	<.001	.37 (.23 – .61)	<.001
No		129/519 (25%)	1		1	
Cholecystectomy prior to or ≤ 3 months after onset of AP (and before RAP)	740					
Yes		35/418 (8%)	.16 (.11 – .24)	<.001	.16 (.11 – .25)	<.001
No		118/322 (37%)	1		1	
Follow-up (years)	740		.99 (.93 – 1.05)	.735		

aLocal complications: parenchymal necrosis, peripancreatic necrosis and/or acute (peripancreatic) fluid collection(s).



Supplementary figure 2A. Preventive measures taken in biliary pancreatitis patients to reduce the risk of recurrence – ERCP

Abbreviations: AP acute pancreatitis, RAP recurrent acute pancreatitis, ERCP endoscopic retrograde cholangio-pancreatography, mo months



Supplementary figure 2B. Preventive measures taken in biliary pancreatitis patients to reduce the risk of recurrence – cholecystectomy

Abbreviations: AP acute pancreatitis, RAP recurrent acute pancreatitis, mo months

Supplementary table S3A. Subgroup analysis of preventive measures taken in biliary pancreatitis patients to reduce the risk of recurrence - ERCP

	Total (n=740)	**No ERCP (n=465)**	**ERCP < 3 mo after AP (n=233)**	**ERCP > 3 mo after AP (n=42)**	**A vs B**	**A vs C**	**B vs C**
No RAP	587 (79%)	378 (81%)	197 (85%)	12 (29%)	P = .287	P < .001	P < .001
RAP	153 (21%)	87 (19%)	36 (15%)	30 (71%)			
RAP before ERCP	N/A	N/A	12 (5%)	24 (57%)			
RAP after ERCP	N/A	N/A	24 (10%)	6 (14%)			

Abbreviations: AP acute pancreatitis, RAP recurrent acute pancreatitis, ERCP endoscopic retrograde cholangiopancreatography, mo months.

Supplementary table S3B. Subgroup analysis of preventive measures taken in biliary pancreatitis patients to reduce the risk of recurrence - cholecystectomy

	Total (n=737)*	**No cholx (n=166)**	**Cholx before or < 3 mo after AP (n=446)**	**Cholx > 3 mo after AP (n=125)**	**A vs B**	**A vs C**	**B vs C**
No RAP	586 (80%)	119 (72%)	382 (86%)	85 (68%)	P < .001	P = .548	P < .001
RAP	151 (20%)	48 (28%)	64 (14%)	40 (32%)			
RAP before cholx	N/A	N/A	29 (7%)	34 (27%)			
RAP after cholx	N/A	N/A	35 (8%)**	6 (5%)			

**Data on cholecystectomy were missing for 3 patients. **Including 8 patients who underwent cholecystectomy prior to their first episode of acute pancreatitis. Abbreviations: AP acute pancreatitis, RAP recurrent acute pancreatitis, cholx cholecystectomy, mo months.*

Supplementary table S4. Subgroup analysis of the effect of smoking on progression to recurrent pancreatitis*

	No RAP	**RAP**	**Total**
Patients who quit smoking	14 (88%)	2 (13%)	16
Patients who continued smoking	15 (58%)	11 (42%)	26
Total	29 (69%)	13 (31%)	42
P = .084			

**Data on smoking were available in 15% (42/276) of the patients who reported current smoking at inclusion.*

Supplementary table S5A. Subgroup analysis of the effect of alcohol consumption on progression to recurrent pancreatitis*

	No RAP	RAP	Total
Alcohol cessation	38 (84%)	7 (16%)	45
No alcohol cessation	102 (76%)	32 (24%)	134
Total	140 (78%)	39 (22%)	179
P = .242			

**Data on alcohol consumption were available in 28% (179/649) of the patients who reported alcohol consumption at inclusion.*

Supplementary table S5B. Subgroup analysis of the effect of alcohol consumption on progression to recurrent pancreatitis stratified for alcoholic etiology

		No RAP	RAP	Total
Alcoholic AP P = .043	Alcohol cessation	8 (89%)	1 (11%)	9
	No alcohol cessation	9 (45%)	11 (55%)	20
	Total	17 (59%)	12 (41%)	29
Non-alcoholic AP P = 1.000	Alcohol cessation	30 (83%)	6 (17%)	36
	No alcohol cessation	93 (82%)	21 (18%)	114
	Total	123 (82%)	27 (18%)	150

Supplementary table S6. Factors associated with chronic pancreatitis – univariate and multivariate analyses (original dataset)

		Univariate analyses			Multivariate analyses with RAP as covariate (n=990)		Multivariate analyses without RAP as covariate (n=990)	
Variable	N	n/N (%)	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (years)	1184		.98 (.96 – .99)	<.001	.99 (.97 – 1.02)	.605	.99 (.97 – 1.01)	.306
Gender	1184							
Male		58/660 (8%)	3.51 (1.94 – 6.37)	<.001	1.97 (.97 – 4.00)	.062	1.89 (.94 – 3.79)	.074
Female		14/524 (3%)	1		1		1	
BMI*	741		.86 (.80 – .92)	<.001				
Etiology	1184			<.001		<.001		<.001
Biliary		13/740 (2%)	1		1		1	
Alcoholic		35/156 (22%)	16.18 (8.32 – 31.46)	<.001	6.46 (2.22 – 18.78)	<.001	7.35 (2.60 – 20.76)	<.001
Idiopathic		16/156 (10%)	6.39 (3.01 – 13.58)	<.001	6.09 (2.57 – 14.41)	<.001	7.15 (3.08 – 16.59)	<.001
Other		8/132 (6%)	3.61 (1.47 – 8.88)	.005	3.08 (1.05 – 9.04)	.040	3.21 (1.12 – 9.16)	.029
Smoking	1029			<.001		.026		.019
Current		40/276 (14%)	5.50 (3.09 – 9.79)	<.001	2.54 (1.23 – 5.27)	.012	2.57 (1.29 – 5.12)	.007
Past		11/151 (7%)	2.55 (1.18 – 5.52)	.018	2.40 (1.02 – 5.66)	.046	2.33 (1.00 – 5.41)	.049
Never		18/602 (3%)	1		1		1	
Alcohol	1066			<.001		.468		.412
Heavy users		22/112 (20%)	11.43 (4.93 – 26.51)	<.001	2.33 (.68 – 7.96)	.178	2.08 (.64 – 6.78)	.226
Excessive users		10/49 (20%)	11.99 (4.47 – 32.15)	<.001	3.47 (.92 – 13.13)	.066	3.24 (.89 – 11.81)	.075
Social users		28/488 (6%)	2.85 (1.28 – 6.32)	.010	1.59 (.66 – 3.81)	.304	1.47 (.62 – 3.50)	.385
Past		3/35 (9%)	4.38 (1.11 – 17.34)	.035	2.29 (.47 – 11.18)	.306	2.86 (.63 – 12.96)	.173
Never		8/382 (2%)	1		1		1	
ASA-classification	1184			.010		0.968		0.988
I		10/225 (4%)	1		1		1	
II		22/520 (4%)	.95 (.44 – 2.04)	.895	.86 (.32 – 2.27)	.755	.91 (.35 – 2.32)	.839

III		40/430 (9%)	2.21 (1.08 – 4.50)	.030	.76 (.25 – 2.27)	.618	.83 (.29 – 2.40)	.724
IV		0/9 (0%)	.00 (.00 –)	.999	.00 (.00 –)	.999	.00 (.00 –)	.999
CRP < 48 hours after admission	1176		1.00 (1.00 – 1.00)	.037	1.00 (1.00 – 1.00)	.915	1.00 (1.00 – 1.00)	.926
Leukocytes < 48 hours after admission	1178		1.01 (.99 – 1.03)	.494				
APACHE II score	1172		.99 (.92 – 1.05)	.647				
Modified Glasgow score	1173		.89 (.73 – 1.10)	.278				
Severity according to Atlanta	1184							
Mild		45/833 (5%)	1					
Moderate/severe		27/351 (8%)	1.46 (.89 – 2.39)	.134				
Pancreatic necrosis	1174							
Yes		17/173 (9%)	1.87 (1.06 – 3.31)	.031	.68 (.25 – 1.82)	.443	.87 (.33 – 2.28)	.776
No		55/1001 (5%)	1		1		1	
Acute (peri-)pancreatic fluid collection(s)	1184							
Yes		26/305 (9%)	1.67 (1.01 – 2.76)	.044	1.14 (.52 – 2.52)	.744	1.02 (.48 – 2.20)	.955
No		46/871 (5%)	1		1		1	
Local complications[a]	1176							
Yes		26/326 (8%)	1.52 (.92 – 2.50)	.103				
No		46/850 (5%)	1					
Persistent organ failure	1184							
Yes		6/82 (7%)	1.24 (.52 – 2.95)	.628				
No		66/1102 (6%)	1					
Pancreatic intervention during first episode	1184							
Yes		14/119 (12%)	2.32 (1.25 – 4.29)	.008	3.02 (1.07 – 8.58)	.038	1.92 (.71 – 5.19)	.201
No		58/1065 (5%)	1		1		1	
Recurrent acute pancreatitis	1184						*Not included*	
Yes		45/301 (15%)	5.57 (3.39 – 9.16)	<.001	5.17 (2.89 – 9.27)	<.001		
No		27/883 (3%)	1		1			
Follow-up (years)	1184		1.06 (.98 – 1.16)	.143				

[a] *Local complications: parenchymal necrosis, peripancreatic necrosis and/or acute (peripancreatic) fluid collection(s).*

Supplementary table S7. Subgroup analysis of the effect of smoking on progression to chronic pancreatitis*

	No CP	**CP**	**Total**
Patients who quit smoking	19 (100%)	0 (0%)	19
Patients who continued smoking	18 (78%)	5 (22%)	23
Total	37 (88%)	5 (12%)	42
P = .530			

**Data on smoking were available in 15% (42/276) of the patients who reported current smoking at inclusion.*

Supplementary table S8A. Subgroup analysis of the effect of alcohol consumption on progression to chronic pancreatitis*

	No CP	CP	Total
Alcohol cessation	46 (90%)	5 (10%)	51
No alcohol cessation	122 (95%)	6 (5%)	128
Total	168 (94%)	11 (6%)	179
P = .298			

**Data on alcohol consumption were available in 28% (179/649) of the patients who reported current alcohol consumption at inclusion.*

Supplementary table S8B. Subgroup analysis of the effect of alcohol consumption on progression to chronic pancreatitis stratified for alcoholic etiology

		No CP	CP	Total
Alcoholic AP P = .633	Alcohol cessation	7 (70%)	3 (30%)	10
	No alcohol cessation	16 (84%)	3 (16%)	19
	Total	23 (79%)	6 (21%)	29
Non-alcoholic AP P = .614	Alcohol cessation	39 (95%)	2 (5%)	41
	No alcohol cessation	106 (97%)	3 (3%)	109
	Total	145 (97%)	5 (3%)	150

Supplementary table S9. Cross-sectional analysis of long-term quality of life and Izbicki Pain Scores in acute pancreatitis patients*

		Recurrent pancreatitis (RAP)			Chronic pancreatitis (CP)		
	Overall (n=370)	**RAP[a] (n=66)**	**No RAP (n=293)**	**P-value**	**CP (n=21)**	**No CP (n=349)**	**P-value**
PCS+ Mean ± SD	49.1 ± 10.3	48.4 ± 10.1	49.3 ± 10.4	.489	48.2 ± 9.3	49.2 ± 10.3	.364
MCS+ Mean ± SD	48.8 ± 10.3	48.0 ± 10.9	49.0 ± 10.2	.760	45.5 ± 12.2	49.0 ± 10.1	.125
	Overall (n=347)	**RAP[a] (n=60)**	**No RAP (n=278)**		**CP (n=18)**	**No CP (n=329)**	
Izbicki Pain score++ Mean ± SD	10.3 ± 16.0	16.2 ± 20.2	8.4 ± 13.5	.004	30.5 ± 28.2	9.2 ± 14.3	<.001

**Data on quality of life were obtained for 370 patients (31%) of whom 77 patients had developed RAP and 21 patients were diagnosed with CP. a11 recurrent pancreatitis patients were not included in these analyses because they have further transited to chronic pancreatitis. +Regression weights derived from normative data of the Dutch general population were used to compute the physical and mental component summaries (PCS and MCS) of the SF-12 (range 0 – 100). Higher scores indicate a better quality of life, whereas a score of 50 represents the mean in the general population.++Scale ranges from 0 to 100 points (increasing scores indicating more pain severity). Questions consist of 4 items: frequency of pain, intensity of pain, use of pain medication and disease-related inability to work.*

CHAPTER 7

Gallstones as a cause in presumed acute alcoholic pancreatitis: *observational multicentre study*

British Journal of Surgery 2024

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ABSTRACT

Background: Data on the incidence and clinical relevance of gallstones in patients with suspected acute alcoholic pancreatitis are lacking and are essential to minimize the risk of recurrent acute pancreatitis. The aim of this study was to assess the incidence of gallstones and the associated rate of recurrent acute pancreatitis in patients with presumed acute alcoholic pancreatitis.

Methods: Between 2008 and 2019, 23 hospitals prospectively enrolled patients with acute pancreatitis. Those diagnosed with their first episode of presumed acute alcoholic pancreatitis were included in this study. The term gallstones was used to describe the presence of cholelithiasis or biliary sludge found during imaging. The primary outcome was pancreatitis recurrence during 3 years of follow-up.

Results: A total of 334 patients were eligible for inclusion, of whom 316 patients were included in the follow-up analysis. Gallstone evaluation, either during the index admission or during follow-up, was performed for 306 of 334 patients (91.6%). Gallstones were detected in 54 patients (17.6%) with a median time to detection of 6 (IQR 0-42) weeks. During follow-up, recurrent acute pancreatitis occurred in 121 of 316 patients (38.3%), with a significantly higher incidence rate for patients with gallstones compared with patients without gallstones (59% versus 34.2% respectively; $p<0.001$), while more patients with gallstones had stopped drinking alcohol at the time of their first recurrence (41% versus 24% respectively; $p=0.020$). Cholecystectomy was performed for 19 patients with gallstones (36%). The recurrence rate was lower for patients in the cholecystectomy group compared with patients who did receive inadequate or no treatment (5/19 versus 19/34 respectively; $p=0.038$).

Conclusions: Gallstones were found in almost one in every five patients diagnosed with acute alcoholic pancreatitis. Gallstones were associated with a higher rate of recurrent pancreatitis, while undergoing cholecystectomy was associated with a reduction in this rate.

INTRODUCTION

The incidence of acute pancreatitis continues to rise, with an average annual increase of 3.67% in the USA (1). Biliary disease and alcohol are the most common causes (2, 3). Identification of the underlying aetiology is important to guide targeted interventions; cholecystectomy can prevent recurrent biliary events in patients with biliary pancreatitis (4), while alcohol cessation support can reduce the risk of recurrent acute pancreatitis (5). Yet, the precise alcohol threshold that defines alcoholic aetiology is unclear and likely varies between patients (6). Previous studies have used different definitions, with thresholds ranging from more than 3 or 4 units per day (7, 8) to more than 4 units in the 24h before onset (9). As a result, the diagnosis often depends on ruling out other potential causes. Current guidelines recommend a comprehensive evaluation that includes a personal and family history, laboratory tests, and a transabdominal ultrasonography (TUS) (10). If TUS shows cholelithiasis, biliary sludge, or dilated bile duct(s), biliary disease is generally considered the most likely cause (11), at least for those who are not excessive drinkers.

Distinguishing between biliary and alcoholic aetiologies can be challenging. First, the lack of clear criteria for alcoholic pancreatitis may lead clinicians to rely on subjective interpretations of excessive alcohol consumption. This approach may bypass TUS, as recommended by the guidelines (10), potentially leading to the misdiagnosis of patients with biliary aetiology as having alcoholic pancreatitis alone. Second, the diagnostic accuracy of TUS in detecting sludge is limited, especially in the acute phase (12, 13). Therefore, patients with suspected idiopathic acute pancreatitis often undergo TUS for a second time and, if necessary, endoscopic ultrasonography (EUS) (9, 14). Conversely, for patients labelled as having alcoholic pancreatitis, the diagnostic work-up may stop after a single (possibly suboptimal) TUS at the time of diagnosis. This scenario exposes patients to potential recurrent biliary events, including acute pancreatitis. Finally, even if a biliary aetiology is identified, it may go untreated because alcohol is considered the primary trigger of pancreatitis. This again raises the risk of future biliary complications.

In the absence of available literature, the aim of this study was to assess the incidence of gallstones and the associated rate of recurrent acute pancreatitis in a large prospective nationwide cohort of patients with presumed acute alcoholic pancreatitis.

METHODS

This study was performed according to the principles of the Declaration of Helsinki and the STROBE guideline (available as Supplementary material) (15). This study was not pre-registered in an independent, institutional registry.

Study design and population

This study is a post-hoc analysis of the Dutch Pancreatitis Study Group's prospective nationwide registry of acute pancreatitis (PWN-CORE). For this study, all patients from 23 hospitals between 2008 and 2019 were screened for eligibility. Acute pancreatitis was defined according to the revised Atlanta classification (16).

Eligible patients were adults with a first episode of 'presumed' alcoholic pancreatitis, diagnosed when the treating physician considered alcohol as the most likely cause, and no treatment was initiated for other aetiological factors. Patients were excluded if they had chronic pancreatitis according to the M-ANNHEIM criteria at the time of the first diagnosis of acute pancreatitis (17), if they had a previous episode of acute pancreatitis for which data could not be retrieved, or if data were incomplete. PWN-CORE was approved by a medical ethics committee (W19.088). Written informed consent was obtained from each participant.

Data collection

Clinical data, including patient characteristics and results of laboratory and imaging tests, were prospectively collected at the time of initial hospitalization using a standardized case record form. Follow-up data on imaging, and readmissions and outpatient hospital visits for recurrent pancreatitis, biliary complications, and biliary interventions were collected retrospectively from medical records and evaluated until 3 years after the initial admission. Only initial admission data were used for patients who were lost to follow-up. Data were imported into data management software by two researchers (N.J.S. and F.E.M.d.R.). Any discrepancies were resolved by discussion with the involvement of an expert (R.C.V.) until consensus was reached.

Outcomes

The primary outcome was the rate of recurrent acute pancreatitis according to the revised Atlanta classification during the 3 years after the initial admission (16). This follow-up interval was chosen because it was not considered feasible to link the initial episode of pancreatitis to subsequent gallstone detection and possible recurrence beyond this interval. Secondary outcomes included biliary events, biliary interventions, adherence to guidelines for performing the standard diagnostic work-up (10), and diagnostic yield of additional imaging after an initial negative TUS result.

Definitions

Alcohol consumption, as reported immediately upon hospital admission, was converted into standard units per week (1 standard unit equals 10 g) for regular drinkers using an online calculation tool (18). Those who occasionally consumed more than 4 (for women) or 5 (for men) standard units were classified as binge drinkers (19). The term gallstones was used to describe the presence of cholelithiasis or biliary sludge found during the following imaging tests: transabdominal TUS, EUS, magnetic resonance imaging (MRI), and magnetic resonance cholangiopancreaticography (MRCP) (14, 20-22). Biliary events included acute cholecystitis, cholangitis, obstructive choledocholithiasis requiring endoscopic retrograde cholangiopancreaticography, and biliary colic. Acute cholecystitis and cholangitis were defined according to the Tokyo classification (23, 24). Biliary colic was defined according to the Rome IV criteria (25). A complete standard diagnostic work-up was defined as serum calcium and triglycerides tests, and imaging with TUS according to the International Association of Pancreatology/American Pancreatic Association guidelines during the index admission (10). Personal and family histories (that is drug use, genetic mutations, etc.) were not included in this study due to the challenges of the retrospective design. All definitions are listed in Table S1.

Statistical analysis

All analyses were performed using SPSS® (IBM, Armonk, NY, USA). Categorical variables are presented as n (%) and continuous variables are presented as mean (s.d.) or median (interquartile range (IQR)). Statistical comparisons between patients with and without gallstones were made using the chi-squared test or Fisher's exact test for categorical data and Student's t-test or the Mann-Whitney U test for continuous data. Other pre-specified subgroup analyses were attempted based on history of cholecystectomy and initial TUS results. The diagnostic yield for each imaging modality is presented as % (95% CI). Missing data were not imputed. $P<0.050$ was considered statistically significant.

RESULTS

Between 2008 and 2019, 2447 patients from 23 hospitals were prospectively registered. Of these, 334 were included in the present study (Figure 1). Clinical characteristics are shown in Table 1. A total of 10 patients (3.0%) had previously undergone a cholecystectomy.

Alcohol consumption was self-reported for 295 patients (Table 1). Median liver enzyme levels at admission are shown in Table 1.

During the index admission, serum calcium tests were performed for 290 patients (86.8%) and triglyceride tests were performed for 199 patients (59.6%). Abnormal calcium and triglyceride tests were found for 0 patients and 16 patients (8.0%), respectively. TUS was performed during the index admission for 276 patients (82.6%). The median number of standard alcohol units per week was higher for the group of patients who did not undergo TUS than in those who did undergo TUS (70 versus 35 units per week; respectively; p<0.001) (Table S2). A complete standard diagnostic work-up according to the guidelines was performed for less than half of all patients (156 of 334 patients (46.7%)).

During the 3-year follow-up interval, 19 patients (5.7%) died (of these, 3 patients died during the index admission). A total of 18 patients (5.4%) were lost to follow-up after the index admission (Figure 1), resulting in 316 patients included in the assessment for the follow-up interval.

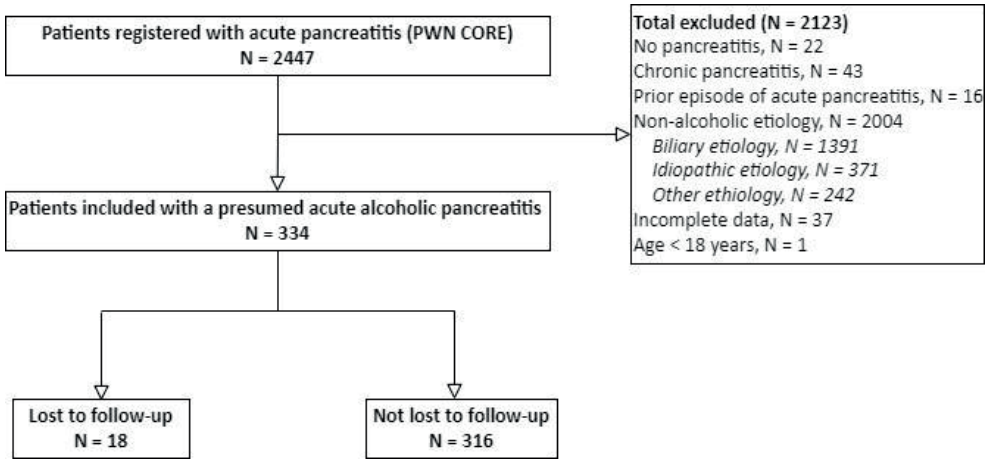

Figure 1. Flowchart

Gallstone detection

During the index admission, 276 out of 334 patients (82.6%) underwent TUS, of whom 18 (6.5%) were found to have gallstones (Table 2). During follow-up, 198 out of 316 patients (62.7%) underwent imaging, including (repeat) TUS for 168 patients (53.2%), MRI/MRCP for 69 patients (21.8%), and EUS for 40 patients (12.7%). These imaging modalities identified gallstones in 47 patients (23.7%). Taking into account overlap, 306 out of 334 patients (91.6%) underwent at least one imaging test for gallstone evaluation, either during the index admission or during follow-up. Gallstones were found in 54 of these 306 patients (17.6%), of whom 1 was lost to follow-up. The median detection time was 6 (IQR 0-42) weeks after the index admission.

Table 1. Clinical characteristics

	N=334
Age in years – mean (SD)	50 (14)
Male sex – no. (%)	275 (82.3%)
BMI – median (IQR) (n=182)	25 (23-28)
Prior cholecystectomy – no. (%)	10 (3.0%)
Self-reported alcohol use per week – no. (%) (n=295)*	
≤21 units	49 (16.6%)
>21 units	188 (63.7%)
Binge drinking	58 (19.7%)
Smoking – no. (%) (n=304)	200 (65.8%)
Liver enzymes at admission – median (IQR)	
Aspartate aminotransferase in U/L (n=324)	39 (25-79)
Alanine aminotransferase in U/L (n=329)	40 (24-72)
Alkaline phosphatase in U/L (n=327)	86 (71-119)
Gamma-glutamyltransferase in U/L (n=330)	113 (52-395)
Bilirubin total in µmol/L (n=329)	14 (9-22)
Standard diagnostic work-up during index-admission	
Calcium testing – no. (%)	290 (86.8%)
Calcium in mmol/L – median (IQR)	2.29 (2.12-2.40)
Calcium >3 mmol/L – no. (%)	0
Triglycerides testing – no. (%)	199 (59.6%)
Triglycerides in mmol/L – median (IQR)	1.53 (0.92-2.80)
Triglycerides >11.2 mmol/L – no. (%)	16 (8.0%)
Transabdominal ultrasound – no. (%)^	276 (82.6%)
Complete standard diagnostic work-up – no. (%)	156 (46.7%)
Severity of acute pancreatitis – no. (%)#	
Mild	207 (62.0%)
Moderate severe	94 (28.1%)
Severe	33 (9.9%)
Mortality – no. (%)	19 (5.7%)
During index admission – no. (%)	3 (0.9%)

*Data are presented as no. (%), mean (SD), or median (IQR). *The cut-off value of 21 units/week was chosen based on the definitions of the Dutch National Institute for Public Health and Environment, which defines excessive alcohol consumption as more that 21 units per week. ^Magnetic resonance cholangiopancreatography was used as the first diagnostic modality in 3 patients. #According to the revised Atlanta classification. Abbreviations: BMI body mass index.*

For the subgroup of patients whose initial TUS during the index admission did not reveal gallstones, the diagnostic yields of subsequent imaging tests are detailed in Table 3. The overall gallstone detection rate was 11.0% (95% CI 7.6-14.4). The individual rates were: 11.5% for repeat TUS, 2.8% for MRI/MRCP, and 23.7% for EUS.

Table 2. Number and yield of imaging tests

Type of test	Patients with imaging test – no. (%)	Patients with gallstones based on imaging test – no. (%)^	Total of imaging tests performed - no	Gallstones demonstrated on first positive imaging– no*
TUS during index admission	276 (82.6%)	18 (6.5%)	276	12 cholecystolithiasis 1 choledocholithiasis 8 sludge in gallbladder 2 sludge in CBD
Imaging tests after index admission	198 (62.7%)	47 (23.7%)	434	37 cholecystolithiasis 2 choledocholithiasis 20 sludge in gallbladder
(Repeat) TUS	168 (53.2%)	40 (23.8%)	300	27 cholecystolithiasis 15 sludge in gallbladder
MRI/MRCP	69 (21.8%)	4 (5.8%)	86	3 cholecystolithiasis 2 sludge in gallbladder
EUS	40 (12.7%)	11 (27.5%)	48	7 cholecystolithiasis 2 choledocholithiasis 3 sludge in gallbladder
Total for all imaging tests	306 (91.6%)	54 (17.6%)	710	49 cholecystolithiasis 3 choledocholithiasis 28 sludge in gallbladder 2 sludge in CBD

*Data are presented as no. (%) or no. ^Multiple positive imaging modalities in one patients were scored as one outcome. *Please not that in several cases multiple biliary findings were observed in a single patient. Abbreviations: Abbreviations: EUS endoscopic ultrasound, CBD common bile duct, MRCP magnetic resonance cholangiopancreatography, MRI magnetic resonance imaging, TUS transabdominal ultrasound.*

Recurrent acute pancreatitis and biliary events

During follow-up, recurrent acute pancreatitis occurred in 121 of 316 patients (38%). Patients with gallstones (31 of 53 (59%)) were significantly more likely to develop recurrent acute pancreatitis than patients without gallstones (90 of 263 (34.2%)) ($p<0.001$). Self-reported alcohol consumption at admission for the first recurrent episode was available for 114 of the 121 patients with recurrence, of whom 32 (28.1%) reported no longer consuming alcohol (41% versus 24% for patients with and without gallstones respectively $p=0.020$). Subgroup analyses, based on the initial TUS results during the index admission, are presented in Table S3 and show recurrence rates of 53% for patients with an initial positive TUS result, 48% for patients who did not undergo TUS, and 35.0% for patients with an initial negative TUS result. Biliary events after the first episode of pancreatitis were observed in nine patients (3%) (cholangitis, 4 patients; acute cholecystitis, 2 patients; obstructive choledocholithiasis, 2 patients; and colic, 1 patient).

Table 3. Number and yield of additional imaging tests in patients with an initial negative US (n=243)^

Type of test	Patients with diagnostic test – no. (%)	Patients with gallstones based on diagnostic test – no. (%)	Total of diagnostic tests performed – no.	Total times gallstones were demonstrated – no.	Diagnostic yield – percentage (95% CI)
Repeat TUS	128 (52.7%)	21 (16.4%)	218	25	11.5% (6.8-15.2)
MRI/MRCP	56 (23.0%)	2 (3.6%)	71	2	2.8% (-1.0-6.6)
EUS	32 (13.2%)	8 (25.0%)	38	9	23.7% (10.1-37.3)
Total	154 (63.4%)	26 (16.9%)	327	36	11.0% (7.6-14.4)

Data are presented as no. (%), no., or percentage (95% CI). ^A total of 15 patients were excluded as they were lost to follow-up. Abbreviations: EUS endoscopic ultrasound, MRCP magnetic resonance cholangiopancreatography, MRI magnetic resonance imaging, TUS transabdominal ultrasound.

Biliary treatment

During follow-up, 22 of 53 patients with gallstones (42%) underwent biliary intervention. The procedures performed were cholecystectomy with or without biliary endoscopic sphincterotomy (ERCP) (19 patients), biliary endoscopic sphincterotomy alone (1 patient), and percutaneous gallbladder drainage (2 patients). The remaining 31 patients (59%) received no biliary intervention. A single patient underwent an unsuccessful ERCP procedure in which no biliary access could be obtained, one patient's scheduled cholecystectomy was cancelled due to the development of metastatic disease, and another patient did not attend a scheduled appointment at the surgical division to discuss the possibility of elective cholecystectomy.

After receiving appropriate treatment (that is cholecystectomy), 5 of 19 patients developed recurrent acute pancreatitis compared with 19 of 34 patients who received inadequate treatment (that is ERCP or percutaneous gallbladder drainage alone) or no treatment (relative risk 0.47; 95% CI 0.21-1.06; p=0.038).

DISCUSSION

In this first nationwide cohort study, we found that 91.6% of patients with presumed acute alcoholic pancreatitis underwent gallstone evaluation, and 17.6% were found to have gallstones. Patients with gallstones had a nearly twofold increased risk of recurrent acute pancreatitis. In contrast, those patients with gallstones who underwent cholecystectomy had half the risk of recurrence. Cholecystectomy was performed for only 36% of patients.

The main findings are that the risk of pancreatitis recurrence significantly increased from 34.2% to 59% in the presence of gallstones for patients with presumed acute alcoholic pancreatitis, even if more of these patients were alcohol abstinent at the time of recurrence. Although the authors' study group has previously evaluated recurrence rates for patients with biliary pancreatitis and alcoholic pancreatitis (26) (rates of 12% and 24%, respectively), no studies have specifically targeted our study population, making direct comparisons difficult. Based on these results, one could speculate that a significant number of patients diagnosed with alcoholic pancreatitis may indeed have biliary pancreatitis, accompanied by excessive alcohol consumption habits, and may benefit from cholecystectomy. The results of the present study show that the recurrence rate after cholecystectomy is indeed two times lower than after no treatment.

A dual role for alcohol in the pathophysiology of acute pancreatitis, acting as either a trigger or a modulator, has previously been suggested (6). This is supported by the low lifetime risk of developing acute pancreatitis in the overall population of excessive alcohol consumers (27). However, the potential interaction of alcohol with biliary disease in the development of acute pancreatitis and vice versa remains far from clear. Furthermore, the authors believe that the exact aetiology cannot be determined when a patient presents with both gallstones and excessive alcohol consumption. Future studies should focus on identifying biochemical and clinical markers and combining them in a (machine learning) prediction model to adequately differentiate between these two aetiologies. Meanwhile, it is important to recognize and address both potential aetiologies, with the initial approach being that patients with excessive alcohol consumption undergo the same diagnostic work-up as non-drinkers.

At admission, current guidelines recommend testing for calcium and triglycerides and performing an TUS (10). In the present study, only half of the patients underwent this recommended work-up. Although TUS is both affordable and non-invasive, it was not performed in 17.4% of patients. Notably, a significant difference in alcohol consumption was observed, favouring patients who underwent TUS. This raises concerns about potential alcohol-related stigma in the management of acute pancreatitis, which should be further explored, for example in a qualitative study assessing the stigmatizing attitudes of pancreatologists towards their patients. Such attitudes have been well documented in other diseases often considered to be self-inflicted, such as HIV, obesity, and psychiatric disorders (28-30). The potential influence of stigma on the doctor-patient relationship, and its impact on a patient's quality of life (31) underscores the need to improve the understanding of the pathophysiology and to establish universally accepted diagnostic criteria for acute alcoholic pancreatitis. In the meantime, strict adherence to guidelines for patients suspected of having alcoholic pancreatitis remains critical, especially as the recurrence rate of pancreatitis was sig-

nificantly higher for patients who did not undergo TUS compared with patients with an initially negative TUS result.

Positive TUS findings for gallstones were present for 6.5% of patients during the index admission, suggesting that an initial diagnosis of just alcoholism would be incorrect. However, given the established prevalence of biliary disease in the general population in the USA (32), these findings must be interpreted with caution. Factors known to increase the risk of biliary disease include female sex, older age, and higher BMI (33), while the effect of alcohol remains controversial (34-36). Alcohol has been associated with gallstones because of its role in lipid metabolism, but studies also report that alcohol may increase gallbladder motility and decrease bile lithogenicity, thus protecting against gallstone formation.

Additional imaging was performed for 62.7% of patients with an initial negative TUS result. The overall yield was 11.0%, which may be an underestimate given the relatively low utilization rates of EUS and MRCP, the two modalities with the highest accuracy for detection of gallstones (37, 38). This supports the hypothesis that patients diagnosed with alcoholic pancreatitis may have undetected occult gallstones. However, the inclusion of patients with a high suspicion of gallstones, as indicated by prior diagnostic tests such as repeat TUS, may have influenced the high individual yield of EUS (23.7%). Nevertheless, the repeat TUS showed a notable yield of 11.5%, above the 10% cut-off considered sufficient for routine use of EUS for patients after the first episode of idiopathic acute pancreatitis (9). In the absence of prospective studies, the validity, futility and optimal timing of additional imaging for patients with excessive alcohol consumption and an initial negative TUS result require further investigation before reliable recommendations can be made.

In the present study, only 36% of patients with gallstones underwent a cholecystectomy, while the remaining patients received no or inadequate treatment (that is ERCP or percutaneous gallbladder drainage alone). This suggests that clinicians often consider gallstones in patients with presumed alcoholic pancreatitis as an incidental finding that does not warrant further treatment, which is concerning, as the incidence rate of recurrent acute pancreatitis after cholecystectomy was 5/19 compared with 19/37 for untreated patients. This finding, together with the consistent evidence for the effectiveness of cholecystectomy in preventing recurrence (4, 39), emphasizes that timely cholecystectomy should be considered once gallstones are identified. Nevertheless, the observed recurrence rate after cholecystectomy highlights the importance of broadening the focus beyond the consideration of cholecystectomy alone. Previous studies have shown that alcohol cessation reduces recurrence to almost 0% (40, 41). However, complete alcohol abstinence is notoriously difficult, as the authors have also

observed. In an earlier Finnish trial, additional alcohol reduction efforts were shown to reduce the risk of recurrent acute pancreatitis (5). Recently, the Dutch Pancreatitis Study Group has initiated the multicentre PANDA trial (42). This trial aims to determine the effectiveness of a structured alcohol cessation support programme in reducing the rate of recurrent acute pancreatitis for patients after their first episode of acute alcoholic pancreatitis when compared with the current standard practice.

The post-hoc design of the present study has limitations, leading to several drawbacks. First, it must be emphasized that the observed association between gallstones and recurrent pancreatitis and between cholecystectomy and recurrent pancreatitis does not imply causality. For example, it was not possible to account for the possibility of different aetiologies for different attacks. Second, data on continued alcohol use or cessation after the first episode of pancreatitis were collected post hoc and only at the time of recurrent episodes. Therefore, it was not possible to perform a multivariable analysis with alcohol use as a potential confounder to compare the primary outcome for patients with and without gallstones. In addition, the study utilized a pragmatic approach to assessing alcohol use, relying on patient self-reporting and making the following distinction: continued alcohol use? (yes or no). Third, it was not possible to reliably assess data on smoking after the first episode of pancreatitis, a factor that could also influence the primary outcome. Fourth, a diagnosis of acute alcoholic pancreatitis was made based on the discretion of the treating physician and therefore no predefined diagnostic work-up was required, which may have introduced bias. On the other hand, the present study reflects what is happening in current clinical practice. Another limitation is that all of the imaging studies performed were evaluated and not just those that were done to assess the presence of gallstones. Also, patients who did not undergo any imaging were included in the subgroup of patients thought to have no gallstones. Finally, subgroup analyses based on gallbladder status were not possible because only 10 out of the 334 patients had a history of cholecystectomy.

CONCLUSION

Our study found that 17.6% of patients diagnosed with acute alcoholic pancreatitis had gallstones, which were significantly associated with a higher rate of recurrent acute pancreatitis. In addition, we show that gallstone evaluation at initial admission was not consistently performed. The same was true for the performance of cholecystectomy once gallstones were identified. This is of concern, especially since our results also showed an almost significant reduction in recurrent pancreatitis after cholecystectomy. With the ever-increasing burden of acute pancreatitis, we strongly recommend better adherence to guidelines for all patients suspected of having acute alcoholic pancreatitis, including performing an transabdominal ultrasound, and considering cholecystectomy for those diagnosed with gallstones.

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Table S1. Definitions

Baseline	
Acute pancreatitis	When two of the following criteria were met: upper abdominal pain, serum lipase concentration (or amylase) ≥ 3 times higher than the upper limit of normal or features of acute pancreatitis on imaging
(Presumed) alcoholic pancreatitis	Acute pancreatitis was classified as 'presumed' alcoholic if the treating physician considered alcohol as the most probably cause, and no treatment was initiated for other etiological factors.
Binge drinking	The term binge drinking was used for women consuming 4 or more standard units on an occasion or 5 or more standard units on an occasion for men
Outcomes	
Gallstones	Gallstones were defined as the presence of cholelithiasis or biliary sludge on the following imaging techniques: transabdominal ultrasound, endoscopic ultrasound, magnetic resonance imaging, and magnetic resonance cholangiopancreaticography
Biliary events	Acute cholecystitis, biliary colic, cholangitis, or obstructive choledocholithiasis
Acute cholecystitis	An acute inflammation of the gallbladder, diagnosed when one item in A, B, and C is present (according to the Tokyo classification): A) Local signs of inflammation 1) Murphy's sign, or 2) Right upper abdominal quadrant mass, pain or tenderness B) Systemic signs of inflammation 1) Fever or hypothermia 2) Elevated C-reactive protein, or 3) Elevated white blood cell count C) Imaging findings characteristics of acute cholecystitis Note: Acute cholecystitis that occurs in the absence of gallstones (i.e. acalculous cholecystitis) did not meet our criteria for acute cholecystitis
Biliary colic	Intermittent pain located in the epigastrium and/or right upper quadrant lasting at least 30 minutes, severe enough to interrupt daily activities or lead to an emergency department visit, not related to bowel movements, and not relieved by postural change or acid suppression (according to Rome IV criteria)

Table S1. Definitions (*continued*)

Cholangitis	An inflammation of the bile duct(s), diagnosed when one item in A, B, and C is present (according to the Tokyo classification): A) Systemic inflammation 1) Fever, hypothermia and/or shaking chills 2) Laboratory data: evidence of inflammatory response (abnormal white blood cell counts, increase of serum CRP levels, and other changes indicating inflammation) B) Cholestasis 1) Jaundice 2) Laboratory data: abnormal liver function tests C) Imaging 1) Biliary dilatation 2) Evidence of aetiology on imaging Note: Cholangitis that occurs in the absence of gallstones did not meet our criteria for cholangitis
Obstructive choledocholithiasis	Presence of gallstones or biliary sludge in the common bile duct on imaging, requiring an ERCP, according to the treating physician
Chronic pancreatitis	A chronic inflammation of the pancreatic parenchyma, defined as typical clinical history or chronic pancreatitis (such as recurrent acute pancreatitis or abdominal pain, except for primary painless pancreatitis and one or more of the following (according to the M-ANNHEIM criteria): A) Pancreatic calcifications B) Moderate or marked ductal lesions C) Marked and persistent exocrine insufficiency D) Typical histology
Complete standard diagnostic work-up	Complete standard diagnostic work-up was defined as laboratory testing, including calcium and triglycerides, and imaging using transabdominal ultrasound, MRI or MRCP (according to IAP/APA guidelines). Note: The standard diagnostic work-up did not include the patient's family history of hereditary pancreatitis or associated genetic mutations, as well as their personal history, such as drug use, due to the challenges of collecting this data retrospectively
Positive imaging	Positive imaging is defined as imaging in which proof of gallstones were found. Note: Isolated dilatation of the intrahepatic bile ducts or CBD was not deemed conclusive evidence for establishing a biliary etiology. This is due to the limitations imposed by the post-hoc design of the study, which prevents reliably confirmation of the absence of other factors that could potentially contribute to duct dilatation, such as stenosis, obstruction caused by external compression, or opioid use
Recurrent acute pancreatitis	Recurrence of acute pancreatitis is defined as a new episode of acute pancreatitis after complete resolution of all symptoms associated with the previous episode (according to the Revised Atlanta criteria)

Table S2. Self-reported alcohol use in patients with and without transabdominal ultrasound at index admission

Self-reported alcohol use per week	All patients (n=295)*	Patients with TUS (n=246)	Patients without TUS (n=49)	P-value
Units – median (IQR) (n=237)^	42 (28-70)	35 (28-70)	70 (35-112)	**<0.001**
≤ 21 units – no. (%)	49 (16.6%)	43 (17.5%)	6 (12.2%)	0.369
> 21 units – no. (%)	188 (63.7%)	155 (63.0%)	33 (67.3%)	0.564
Binge drinking – no. (%)	58 (19.7%)	48 (19.5%)	10 (20.4%)	0.885

*Data are presented as no. (%), or median (IQR). *The levels of self-reported alcohol use were available in 295/334 patients. ^The 58 patients who met the definition for binge drinking were excluded to calculate the median self-reported alcohol use per week. Abbreviations: TUS transabdominal ultrasound.*

Table S3. Subgroup analyses of recurrent acute pancreatitis

	All patients (n=316)^	**Patients with positive first TUS (n=17)[A]**	**Patients with negative TUS (n=243)[B]**	**Patients with no TUS (n=56)[C]**	**P-value**	
					A vs. B	**B vs. C**
Recurrent acute pancreatitis	121 (38.3%)	9 (52.9%)	85 (35.0%)	27 (48.2%)	0.136	0.065

Data are presented as no. (%). ^A total of 18 patients were excluded as they were lost to follow-up . Abbreviations: TUS transabdominal ultrasound.

CHAPTER 8

Alcohol reduction to reduce relapse in acute alcoholic pancreatitis – missed opportunities

Alcohol and Alcoholism 2021

Authors

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ABSTRACT

Aim: Resuming drinking is a main contributant to recurrence in alcoholic pancreatitis. We assessed current clinical practice in the Netherlands regarding alcohol in managing patients with a first episode of acute alcoholic pancreatitis.

Methods: A survey was distributed to 35 hospitals affiliated with the Dutch Pancreatitis Study Group. We evaluated current support based on various components of brief interventions, the participation of psychosocial healthcare providers, the cooperation with the primary care physicians and the presence of a protocol and its implementation.

Results: The response rate was 100% (n = 35). Psychoeducation was the most frequently performed intervention in current support treatment (87% of hospitals). In 17% of hospitals, healthcare providers with a psychosocial background routinely participate in current support treatment, 37% of hospitals create an individual treatment plan in which goals regarding alcohol cessation are specified and only 46% of hospitals provide the primary care physician with specific discharge information; 31% of hospitals indicate that the treatment is uniformly performed within their division of Gastroenterology. Protocols are available in 3% of the hospitals surveyed. Opportunities to involve the patient's social network were not given sufficient priority.

Conclusion: Among Dutch hospitals, there is no routine management strategy with regard to enhancing treatment for heavy alcohol use in alcoholic pancreatitis patients. There is a need to test a validated support program in randomized studies. Meanwhile, possible opportunities for effecting change are often missed.

INTRODUCTION

Approximately 1300 patients per year with a first episode of acute alcoholic pancreatitis are admitted to the hospital in the Netherlands (1, 2). Acute alcoholic pancreatitis can vary from a mild (80% of patients) to a severe and even life-threatening disorder (20% of patients). Severe complications of acute pancreatitis include (infected) pancreatic necrosis and multiple organ failure (3).

A Dutch cross-sectional study has shown that 25% of patients after a first episode of alcoholic pancreatitis have at least one recurrent attack and 16% develop chronic pancreatitis (4). Continuation of alcohol consumption is the most important modifiable risk factor for the development of this type of recurrent and chronic pancreatitis (4, 5). Although cessation of alcohol use can reduce the recurrence rate of alcoholic pancreatitis to near 0% (6, 7), it is notoriously difficult to stop harmful drinking without treatment. Nonetheless, effective treatments – with small to moderate effect size compared to no treatment – are available and include brief interventions (8). These interventions focus on the patient's context of harmful drinking, the patient's motivation to change drinking behaviour and on achievable individual treatment goals which might include cessation or reduction of alcohol consumption or change in drinking habits (9-11).

Unfortunately, international evidence-based guidelines on the treatment of acute alcoholic pancreatitis (12, 13) make no statements on enhancing treatment for heavy alcohol use and its timing (14). Currently, there is increasing evidence that brief interventions during an admission related to harmful drinking result in significant reduction of alcohol consumption (15, 16). This effect can be explained by the large impact of hospitalization, making patients motivated for cessation and interventions more successful. Only one randomized controlled trial (RCT) has studied the effect of a repeated program (at 6 months-interval) with brief interventions to assist in alcohol cessation specifically in patients with alcohol induced pancreatitis. In this study, a 61.9% reduction was observed in pancreatitis recurrence (from 21% to 8%) in patients receiving a repeated intervention when compared with a single session in-hospital intervention (17).

The fact that the incidence of recurrent alcoholic pancreatitis is still 25%, costing ~1.75 million euros yearly, emphasizes the need to develop a validated alcohol cessation support program for patients with alcoholic pancreatitis, in order to reduce recurrence of alcoholic pancreatitis (4, 18). In addition, continuation of (heavy) alcohol use is not only detrimental to the pancreas, it is also associated with a large social burden and the development of cancer and liver, cerebral and cardiovascular diseases (19).

Therefore, it is crucial to address alcohol use at the time when patients are receptive to change lifestyle, namely during the clinical admission of acute alcoholic pancreatitis. However, little is known about current support treatment regarding alcohol cessation, both during admission and after discharge, in patients diagnosed with acute alcoholic pancreatitis. To gain insight into current practice and to assess whether improvements can be made, this nationwide survey study was conducted.

MATERIAL AND METHODS

In June 2020, the Dutch Pancreatitis Study Group (DPSG) designed an online survey with 13 closed questions, as listed in the Supplementary Material. The DPSG is a nationwide study group of clinical experts and researchers involved in pancreatitis care and is known for conducting high-quality research (3, 20-24). The survey included questions about current support treatment for a 'typical' patient with initial admission for acute alcoholic pancreatitis (mild pancreatitis episode, according to the Revised Atlanta Criteria, with a mean hospital stay of 5 days) (13). We evaluated current support treatment based on different components of brief interventions (i.e. providing information about the harmful effects of drinking alcohol and the existence of self-help organisations), the type of engaged professionals (i.e. consultation of a psychosocial healthcare provider), the treatment setting (i.e. attendance of patient's social network), the discharge planning (i.e. communication of a primary care physician) and the presence of a protocol and its implementation. In this survey, psychosocial healthcare providers include medical psychologists and social workers, as in-hospital consultation for psychosocial problems in the Netherlands is most commonly performed by these professionals. The psychologist is able to diagnose and treat alcohol use disorders, whereas the social worker focuses more on practical support and advice. The respondents surveyed were able to answer the survey with 'yes', 'no' or 'I do not know'.

The survey was sent by an e-mail to 35 divisions of Gastroenterology in hospitals affiliated with the DPSG, as in the Netherlands, patients with an alcohol induced pancreatitis are almost always admitted to the gastroenterology ward instead of the surgery or internal medicine ward (2). Two reminders were sent in June and July 2020 to achieve a high response rate.

Data analyses were performed in SPSS and all data are presented in number and percentage for categorical variables.

RESULTS

The survey response rate was 100% (35/35). There was representation from academic hospitals (n=8), training hospitals (n=24) and regional hospitals (n=3).

Brief intervention during admission

In the vast majority of hospitals (34/35, 97%), the treating physician (i.e. gastroenterologists or residents) informed the patient about the harmful effect of alcohol consumption on the pancreas. Support organizations such as the Alcoholic Anonymous Netherlands were discussed with patients in 30 hospitals (86%). The patient's social network (i.e. partner, family or friend) was invited to attend the educational consultations between the patient and treating physician in 23 hospitals (66%).

Involvement of other care providers

During admission, 16 hospitals (46%) called the primary care physician to obtain background information regarding the patient. In six hospitals (17%), a healthcare provider with a psychosocial background (i.e. medical psychologist or social worker) routinely visited the patients for a clinical consultation. In four of these six hospitals, both medical psychologists and social workers met patients with an alcoholic pancreatitis for a face-to-face consultation. In the remaining two hospitals, patient's consultation was only performed by a medical psychologist. In 11 hospitals (31%) a healthcare provider with a psychosocial background did participate in the support treatment, however face-to-face consultations with patients was not part of standard care. In 18 hospitals (51%), neither the medical psychologists nor the social workers were routinely involved in the support treatment of patients with an acute alcoholic pancreatitis.

Discharge planning

Before discharge, 13 hospitals (37%) created a treatment plan in which goals with regard to alcohol cessation or reduction were specified in concordance with the patient. A total of 16 hospitals (46%) provided specific advice to the primary care physician for the post-hospital care. In addition to the written discharge summary, oral discharge communication to primary care physicians was given by 13 hospitals (37%).

Current implementation

In the majority of hospitals (97%), the treatment strategy of patients with alcoholic pancreatitis with regard to alcohol cessation is not structured in a protocol. In total, 13 responders (37%) indicated that the treatment is not uniformly performed within their department of Gastroenterology. Of the remaining responders, 11 (31%) indi-

cated that the treatment is uniformly performed and 11 (31%) indicated that they did not know the answer.

DISCUSSION

The aim of this nationwide survey was to evaluate current interventions regarding alcohol use in patients diagnosed with a first episode of acute alcoholic pancreatitis. Supportive treatment of alcohol cessation is important, as abstinence or controlled use can prevent recurrence of alcoholic pancreatitis (6, 7). Given that admission for acute alcoholic pancreatitis provides a teachable moment for patients (15), it seems crucial that intervention should start during clinical admission. Despite the fact that gastroenterologists treat many patients with alcohol-related diseases (i.e. pancreatitis, gastrointestinal cancer and liver diseases including cirrhosis), this study demonstrate that (inter)national guidelines on problematic alcohol use are not well implemented (9-11).

According to these guidelines, brief in-hospital intervention is recommended in all patients with an identified alcohol problem. Brief intervention usually includes psychoeducation and motivational interviewing (MI) (11). Aspects of psychoeducation are providing education about the harmful effects of drinking alcohol and the existence of self-help organizations. This provides patients with the ability to make informed decisions regarding alcohol cessation (25). We demonstrate that the majority of hospitals already use psychoeducation through education conversations frequently.

MI is the second intervention that should take place, as it is more effective than psychoeducation (26). MI is often a brief intervention of a maximum of 30 min that focuses on increasing the patient's intrinsic motivation, which enhances behavioural change and stimulates seeking for further treatment, for example in the setting of primary care. Previous studies showed that in-hospital motivational interventions are effective in reducing alcohol consumption and this also applies to patients who did not ask for help (27). The success of MI depends on the interviewer's experience and technique and can be improved by training (28, 29). In addition, the type of professional providing MI seems to have less influence on the effect of MI (30), but providing training seems essential as this enhances success. Remarkably, healthcare providers trained for psychosocial interventions and available for consultations in hospitals (i.e. psychologists and social workers) are actively engaged regarding alcohol cessation support only in the minority of responding hospitals. The percentage is even lower when it involves a face-to-face consultation between the psychologist or social worker and the patient (17%). Hence, clinical practice frequently consists of solely

treating pancreatitis while omitting brief interventions to treat heavy alcohol use. Although much effort is put into optimizing the treatment of biliary pancreatitis with the aim of preventing recurrent biliary attacks, patients with alcoholic pancreatitis are not provided with a brief intervention including MI for their problematic alcohol use. This results in leaving patients at risk of resuming drinking after discharge and further harm (8).

Another prerequisite for good support for alcoholic pancreatitis patients is the involvement of patient's social network (i.e. family, partner or friend), as it increases the treatment success (31, 32). Despite this, the social network is invited to attend the (educational and motivational) interventions in 65% of hospitals. Moreover, this study shows that communication from hospitals to primary care physicians can be improved, both during admission and before discharge. The primary care physician has a longstanding relationship with the patient, therefore being aware of other (alcohol-related) health and mental problems, previous alcohol cessation attempts of the patient and the context of the harmful drinking. We show that about half of the hospitals surveyed consult the primary care physician for background information of the patient. To ensure continuity of care in the home phase, primary care physicians should be informed about the admission and reason for admission and what has been discussed with the patient during in-hospital counselling. Finally, it needs to be underlined that primary care physicians are potential key players in alcohol cessation support in the post-hospitalization setting (33). However, we show that primary care physicians receive concrete (usually written) discharge information from only half of the hospitals.

Lack of uniformity in the implementation of support treatment is also indicated by the majority of respondents. In addition, a standardized protocol for the treatment of patients with alcoholic pancreatitis is available in only one hospital. This might imply the need for a standard and validated protocol.

Potential barriers to implement a nationwide alcohol cessation support program on the level of healthcare professionals may include lack of time, lack of training and doubts about its efficacy. To overcome these barriers, well-designed preferably randomized trials, in which positive health benefits of brief interventions are demonstrated, are needed in order to create support for implementation of an alcohol cessation support program. Barriers among patients may include resistance to accept the need for alcohol counseling, as drinking is often socially accepted and most patients do not recognize the harmful effects of alcohol. Organizational barriers may be the multidisciplinary nature of an alcohol cessation support program and that an 'one-size-fits-all' program might not be suitable for every patient. Despite all barriers, the fact that in-hospital

counseling for alcohol use is part of Dutch insured care can act as a facilitator of implementation.

The strength of this study is the response rate of 100%, which might be a reflection of the importance of this topic felt by gastroenterologists. As we included academic hospitals, teaching hospitals and regional hospitals, our results reflect current clinical practice regarding support for alcohol use in all practice settings, despite the small sample size.

This study also has some limitations. First of all, one limitation is the inclusion of divisions of Gastroenterology with a specific interest in pancreatitis that may be more motivated in treating alcoholic pancreatitis. Therefore, the different aspects of current practice evaluated in our study, such as engaging psychosocial healthcare providers or patient's family during clinical admission and making discharge phone calls to the primary care physician, may be overestimated. Second, this survey was limited to hospitals from the Netherlands only. As no international literature is available on this topic, insight in the current practice on supportive treatment for problematic alcohol use in alcoholic pancreatitis patients from other countries remains unclear. Third, the population of patients with alcoholic pancreatitis is very heterogeneous. For this reason, it was sometimes difficult for the respondents to answer questions about current practice.

CONCLUSION

This national survey study shows suboptimal implementation of brief interventions for alcohol use and insufficient discharge planning for patients diagnosed with alcoholic pancreatitis. These findings accentuate that improvements for supportive treatment of alcohol use can be made. Future studies should determine whether implementation of a multidisciplinary alcohol cessation support program can reduce pancreatitis recurrence in patients with both mild and severe alcoholic pancreatitis. The results of this survey study can help the design of a prospective randomized trial.

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Supplementary file S1. Survey

Q1. Is discussing the relationship between pancreatitis and alcohol use with the patient a routine treatment step?

a) Yes
b) No
c) I do not know

Q2. Is the patient's social network (family, partner etc.) routinely invited to attend the educational consultations between patient and treating physician?

a) Yes
b) No
c) I do not know

Q3. Is the medical psychologist routinely involved in the support treatment during an admission of acute alcoholic pancreatitis?

a) Yes
b) No
c) I do not know

Q4. If yes, does the medical psychologist routinely physically visit the patient during admission?

a) Yes
b) No
c) I do not know

Q5. Is the social worker routinely involved in the support treatment during an admission of acute alcoholic pancreatitis?

a) Yes
b) No
c) I do not know

Q6. If yes, does the social worker routinely physically visit the patient during admission?

a) Yes
b) No
c) I do not know

Q7. Is the general practitioner routinely called to obtain background information about the patient?

a) Yes
b) No
c) I do not know

Q8. Is discussing support organizations as the Alcoholic Anonymous (AA) Netherlands a routine treatment step?

a) Yes
b) No
c) I do not know

Q9. Before discharge, is a treatment plan in which goals regarding alcohol cessation of reduction are specified routinely created in concordance with the patient?

a) Yes
b) No
c) I do not know

Q10. In addition to the written discharge summary, is the general practitioner routinely informed by telephone before discharge?

a) Yes
b) No
c) I do not know

Q11. Is advice routinely given to the general practitioner with regard to the post-hospital care?

a) Yes
b) No
c) I do not know

Q12. Are the treatment steps mentioned above uniformly performed within your department of Gastroenterology?

a) Yes
b) No
c) I do not know

Q13. Does your department have a protocol for alcohol support treatment for alcoholic pancreatitis?

a) Yes
b) No

CHAPTER 9

Structured alcohol cessation support program versus current practice in acute alcoholic pancreatitis (PANDA): *study protocol for a multicenter cluster randomized controlled trial*

Pancreatology 2023

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ABSTRACT

Background/objectives: The most important risk factor for recurrent pancreatitis after an episode of acute alcoholic pancreatitis is continuation of alcohol use. Current guidelines do not recommend any specific treatment strategy regarding alcohol cessation. The PANDA trial investigates whether implementation of a structured alcohol cessation support program prevents pancreatitis recurrence after a first episode of acute alcoholic pancreatitis.

Methods: PANDA is a nationwide cluster randomized superiority trial. Participating hospitals are randomized for the investigational management, consisting of a structured alcohol cessation support program, or current practice. Patients with a first episode of acute pancreatitis caused by harmful drinking (AUDIT score >7 and <16 for men and >6 and <14 for women) will be included. The primary endpoint is recurrence of acute pancreatitis. Secondary endpoints include cessation or reduction of alcohol use, other alcohol-related diseases, mortality, quality of life, quality-adjusted life years (QALYs) and costs. The follow-up period comprises one year after inclusion.

Discussion: This is the first multicenter trial with a cluster randomized trial design to investigate whether a structured alcohol cessation support program reduces recurrent acute pancreatitis in patients after a first episode of acute alcoholic pancreatitis, as compared with current practice.

INTRODUCTION

Alcohol is considered the second leading cause of acute pancreatitis in the Western world, responsible for approximately 20% of cases of acute pancreatitis (1). The prevalence of recurrent acute pancreatitis (ranging from 18% to 46%) and chronic pancreatitis (ranging from 13% to 26%) is high in patients recovered from their first episode of alcoholic pancreatitis (2-11). Continued alcohol use is considered the main preventable risk factor for developing these events (2, 9, 11-13). Harmful drinking brings a large physical and psychosocial burden for patients as well as a financial burden for society (14, 15). Therefore, alcohol cessation should be as much a priority in treating acute alcoholic pancreatitis as cholecystectomy in acute biliary pancreatitis.

There is increasing evidence that (brief) motivational interventions (MI) to assist in alcohol cessation are effective, particularly when performed in a hospital setting (16, 17). The rationale for this success lies in the impact of hospitalization, making patients aware of their underlying alcohol problem and increasing motivation to change. Although guidelines recommend ''dedicated" follow-up visits after acute alcoholic pancreatitis, no guidance is available on the optimal content of this follow-up treatment (18). Therefore, the opportunity to perform MI in this patient group is often missed, placing this group at risk for further harm (19).

To date, one single-center randomized controlled trial (RCT) has studied the effect of in-hospital repeated versus single-session MI on alcohol cessation in acute alcoholic pancreatitis patients (20). In this study by Nordback et al., a 61,9% reduction was observed in pancreatitis recurrence in favor of patients receiving a second MI at a six month-interval. Although this reduction of pancreatitis recurrence is impressive, the extra scheduled visit to the outpatient clinic might be difficult to adopt in every healthcare system, and might also overlook the distinct and potential value of the general practitioner, who has a long-standing relationship with the patient and unique experience in cessation support. Moreover, in this traditional RCT design (20), only patients meeting a certain threshold level of motivation to quit or reduce alcohol use were likely to willing to participate, which may have led to an overestimation of the treatment effect. Finally, the effect of alcohol cessation on quality of life, QALYs and costs have not been studied.

The fact that the incidence of acute alcoholic pancreatitis is still on the rise (21, 22), and no cost-effective prevention programs have yet been described in international guidelines, warrants the need for new evidence. The multicenter cluster randomized PANDA trial aims to determine whether a structured alcohol cessation support program in patients with a first episode of acute alcoholic pancreatitis is superior to

the current practice with regard to recurrent acute pancreatitis. We hypothesize that enhanced efforts aimed at reducing alcohol use, by providing a structured program including an in-hospital MI, reduces the risk of pancreatitis recurrence in these patients and therefore reduces readmissions and costs, and improves quality of life, as compared to the current practice.

METHODS

This trial protocol is written in accordance with the Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) guidelines (23).

Design

PANDA is a multicenter two-level cluster randomized superiority trial with an equal allocation ratio. To date, 33 Dutch hospitals are participating in the trial, including academic hospitals, large teaching hospitals and regional hospitals, each representing one cluster. Before participation, all potential hospitals must complete a survey about their current support treatment during the initial admission for their patients with acute alcoholic pancreatitis (19), and hospitals that already implemented an alcohol cessation support program similar to our intervention program are excluded. The participating clusters will be stratified by type of hospital (academic versus non-academic) and in the case of hospitals with multiple physical locations, all locations will be included in the same cluster.

Study population

The subjects of this trial are hospitalized adult patients with a first episode of acute pancreatitis, according to the Revised Atlanta Criteria (24). The Alcohol Use Disorders Identification Test (AUDIT) (see additional file 1), a 10-item screening tool in the validated Dutch translation, is to be performed in all patients to detect harmful drinking (25). All patients are screened for other potential etiologies by the standard diagnostic work-up as described in the International Association of Pancreatology (IAP)/ American Pancreatic Association (APA) guidelines of 2013 (see additional file 2 and 3) (18). Patients who fulfil the eligibility criteria will be informed about the trial.

The inclusion criteria are:

1. First episode of acute pancreatitis requiring admission
2. AUDIT score >7 for men and >6 for women, indicating likelihood of harmful drinking
3. Age of 18 years or older

4. Written informed consent for participation

The exclusion criteria are:
1. Diagnosis of any etiology other than alcoholic
2. AUDIT score >15 for men and >13 for women, indicating likelihood of alcohol dependence
3. Chronic pancreatitis (according to the M-ANNHEIM criteria) (26)
4. Non-Dutch speaker

All included patients are treated according to the protocol of the treatment arm of the hospital to which they are admitted.

Intervention arm

The alcohol cessation support program is based on the guideline ''Problematic Alcohol Use" of the Dutch College of General Practitioners and the guideline ''Alcohol Use Disorders" of the Dutch Psychiatric Association and consist of five components, see below (27, 28). The program will be carried out by a multidisciplinary team of clinicians (i.e. gastroenterologists and surgeons), psychosocial healthcare providers available for in-hospital consultation whom are already trained for psychosocial interventions (i.e. psychiatrists, psychiatric nurses, medical psychologist and social workers) and primary care physicians. All the clinicians and psychosocial healthcare providers will be offered motivational interviewing training, as MI training is essential for providing MI effectively (29). This 4-h interactive training is given by one experienced MI trainer, who is also an addiction psychologist, and focusses on the four processes of MI including engaging, focusing, evoking and planning. To homogenize the program, the research group has compiled a standard operation procedure (SOP) (see additional file 4). Therefore, the overall framework will be identical in all study sites; however, some details may differ between sites because of logistic reasons or different local protocols.

1. *Medical phase:* if applicable, the clinician optimizes medical treatment of the effects of alcohol use, i.e. supplementation of vitamins and treatment of withdrawal symptoms.
2. *Education phase:* the clinician provides the patient with psychoeducation, including information on the relationship between alcohol use, acute pancreatitis and relapses, and give the following advice: stop drinking alcohol completely and seek for supportive treatment in primary care. A brochure '*Everything you need to know about alcohol'* from the Trimbos Institute, Netherlands Institute of Mental Health and Addiction, is also provided (30).
3. *Motivational phase:* the psychosocial healthcare provider provides a patient-centered intervention following the principles of motivational interviewing: listen with empathy, develop discrepancy between patient's drinking behavior and

goals, adjust to patient's resistance, support their self-efficacy and respect their autonomy. The primary task is to elicit patient's motivation to change drinking behavior and seek for further treatment in the setting of primary care.

4. *Discharge phase:* the clinician contacts the patient's primary care physician by telephone before discharge to ensure continuity of care. This verbal communication must include information about the reason for hospitalization, the medical treatment provided, the patient's harmful behavior of drinking and his or her motivation to change this behavior.
5. *Home phase:* the study coordinator informs the patient's primary care physician about their enrolment in the PANDA by sending a letter. This letter focusses on the awareness of their own guidelines ''Problematic alcohol use" and to promote adherence of this guideline.

Control arm

Current practice has been described in the previously published survey (19). This survey among 35 Dutch hospitals showed a lack in clear protocols for the treatment of acute alcoholic pancreatitis patients and a lack of uniformity in the approach of this treatment within the departments of gastroenterology. In 17% of hospitals, psychosocial health care providers were routinely engaged in the treatment process. In the control arm, usual care will be provided at the discretion of the clinicians.

Primary endpoint

The primary endpoint is recurrence of acute pancreatitis (irrespective of etiology) within 1 year after inclusion. Recurrence of acute pancreatitis is defined as a new episode of acute pancreatitis after complete resolution of all symptoms associated with the previous episode, as defined by the 2013 revised Atlanta criteria (24).

Secondary endpoints

Secondary endpoints are cessation of alcohol use (modified AUDIT score of 0 at any time point during follow-up), clinically relevant reduction of alcohol use (modified AUDIT score ranging between 1 and 7 (men) or 1 and 6 (women) at any time point during follow-up), AUDIT-score at 1 year follow-up, self-reported alcohol use, development of other alcohol-related diseases, mortality, quality of life, QALYs and total direct and indirect costs. The AUDIT questionnaire is modified during follow-up to provide adequate information to assess the first two secondary endpoints, since this questionnaire includes questions regarding the alcohol use behavior in the past year. Therefore, all questions in the questionnaire at 3, 6 and 9 months follow-up are modified to only apply to the period after inclusion (see additional file 5).

Sample size

The sample size was calculated to detect a reduction in the recurrence rate of 62% from 25% in the control arm to 10% in the intervention arm. A recurrence rate of 25% for current practice is based on previous Dutch Data (2). The expected 62% reduction in favor of the intervention arm is based on the RCT from Nordback et al. (20). The sample size was calculated with a two-sided significance level (α) of 0.05, a power of 80% and an intra-cluster correlation of 0.05, which is often used in cluster RCTs. A drop-out rate of 10% was chosen based on previous research of the Dutch Pancreatitis Study Group (DPSG) in which the drop-out rate was less than 5% (31-36). The required sample size for different numbers of participating hospitals (i.e. clusters) are displayed in table 1. Assuming 33 participating hospitals, this will result in a sample size of 320 patients.

Table 1. Sample size

Number of clusters	N per cluster	N
27	13	351
28	12	336
30	11	330
32	10	320
35	9	315
38	8	304
42	7	294

Ethics

The PANDA is conducted in accordance with the 2013 Declaration of Helsinki and Guideline for Good Clinical Practice. The need for ethical approval was waived by the Medical Ethics Committees United (MEC-U). In addition, local board approval will be obtained from all the participating hospitals (see additional file 6).

Statistical aspects

All included patients will be evaluated for primary and secondary endpoints at one year after inclusion. The primary analysis is based on intention-to-treat principles. All analysis will be performed in SPSS or RStudio. A two-sided p value lower than 0.05 is considered statistically significant.

Baseline variables are age, sex, body mass index (BMI), American Society of Anesthesiologist's (ASA) classification, previous alcohol-related comorbidities, AUDIT score, nicotine use, severity of acute pancreatitis, length of hospital admission, motivation to change drinking habits and confidence in ability to change (scale 1-10). Categorical

data will be presented in number and percentage and numerical data as mean with standard deviation (SD) or in case of a skewed distribution as median with interquartile range (IQR).

The primary endpoint, recurrence of acute pancreatitis, will be presented as number with percentage. In subgroup analysis, the Chi-square test or the Fisher's exact test with 95% confidence interval (CI) will be used. A subgroup analysis will include predictors for the primary endpoint (sex, other alcohol-related comorbidities, AUDIT score, nicotine use, severity of acute pancreatitis and motivation level). If the subgroups differ statistically significant in one or more baseline variables, this will be adjusted in a logistic regression analysis.

Secondary endpoints will be presented as number with percentage with 95% CI, as mean with SD or median with IQR. For categorical data (cessation of alcohol use, clinically relevant reduction of alcohol use, development of other alcohol-related diseases, mortality), the Chi-square test of the Fisher's exact test will be used. For numerical data (quality of life, AUDIT score, self-reported alcohol use), the (un-) paired *t*-test, Mann-Whitney *U* test will be used. For quality of life, subgroup analysis will be made for patients with and without pancreatitis recurrence, who achieved and not achieved cessation or clinically relevant reduction of alcohol use.

The economic evaluation will compromise a cost-effectiveness analysis and a cost-utility analysis. The primary endpoint in the cost-effectiveness analysis, are the cost per prevented pancreatitis recurrence. Other medical costs generated in hospitals, resource utilization outside of the hospitals and production loss will also be assessed using the Medical Consumption Questionnaire (MCQ) and Productivity Cost Questionnaire (PCQ). For the cost-utility analysis, costs per additional QALY will be measured using the EQ-5D.

DISCUSSION

Acute alcoholic pancreatitis has a high recurrence rate as it is notoriously difficult to stop harmful drinking (6, 9, 11), which puts patients at increased risk for severe acute pancreatitis, chronic pancreatitis and pancreatic malignancies. Previous research has suggested that in-hospital motivational interventions are effective in reducing the risk of pancreatitis recurrences (20). The PANDA trial is the first cluster randomized controlled trial designed to determine whether implementation of a structured alcohol cessation support program improves the rate of recurrent acute pancreatitis after a follow-up period of one year when compared to current practice.

Previously, it has been shown that cessation of alcohol prevents against recurrent acute alcoholic pancreatitis (9, 11). In two Finnish studies, no recurrent attacks have been observed in patients who achieved abstinence after the first episode while respectively, 33% and 34% of non-abstainers developed at least one relapse. Other risk factors associated with recurrences were younger age and mild severity of the initial episode (10). Notably, another study has suggested that the disease course of acute pancreatitis may affect the patients' motivation for behavior change, since two-thirds of patients who survived a severe attack reduced their excessive alcohol use or achieved abstinence (37). In line with this theory, the impact of an admission related to alcohol may also provide a teachable moment for patients, making them more receptive to change through MI. MI is an intentionally directive counselling approach to elicit intrinsic motivation within a patients to achieve behavior change, while maintaining the patient's autonomy. In MI, patients are encouraged to explore the cons of continuing current behavior and the pros of behavior change, and if ambivalence is evident, supported to move in the direction of change (38). This approach, introduced by Miller and Rollnick (39), and initially developed to treat alcoholism in addiction care, is now widely used in the treatment of many lifestyle problems, also in the hospital setting (40-42). There are several systematic reviews and meta-analyses reporting on the effect of brief in-hospital MI in heavy alcohol users and found that interventions are beneficial regarding alcohol use, alcohol-related injuries and mortality during a follow-up time of 6 to 12 months (17, 43). Therefore, (inter)national guidelines recommend brief MI in the hospital setting in all patients with harmful drinking (27, 28, 44). A recent national survey performed prior to this trial showed that face-to-face consultations between hospitalized acute alcoholic pancreatitis patients and psychosocial healthcare providers was part of standard care in only 17% of hospitals (19). Thus, in current practice MI is suboptimally implemented. Since the success of MI is associated with skills and acknowledge acquired through MI training (45, 46), training and involving psychosocial healthcare providers seems crucial.

The rate of pancreatitis recurrences was significantly less in the repeated-intervention arm of the previously mentioned RCT of Nordback et al. compared to the control arm (single-intervention arm), but the reported alcohol consumption did not differ between the two arms (20). The authors described the difficulties that they experienced evaluating alcohol consumption, since several of the subjects did not want to keep a diary for a period of two years. To overcome this problem, the Timeline Followback method is used to retrospectively assess the number of drinking days and the total amount of drinks consumed in the past 2 weeks at five time points (47). Furthermore, quality of life, QALYs and costs were not evaluated in this study. PANDA will be the first trial assessing whether a structured alcohol cessation support program prevents pancreatitis recurrence, to further reduce cost and improve quality

of life, in which the continuing alcohol consumption level after diagnosis is strictly monitored through 3-monthly validated questionnaires.

It is not clear which level of alcohol intake determines whether the most likely etiology is alcoholic pancreatitis (48-55). Multiple undefined criteria for acute alcoholic pancreatitis are used in literature, such as excessive alcohol use, alcohol misuse, heavy alcohol use, binge-drinking *et cetera* (9, 11). In some studies, the limit of alcohol intake was set at four units in the last two days prior to the start of acute pancreatitis (56, 57). For PANDA, we used the validated AUDIT-questionnaire as a screening tool (25). Patients that scored an AUDIT between 8 and 15 (for women between 7 and 13), suggesting a strong likelihood of harmful drinking, will be eligible to enroll. In patients with harmful drinking behavior and acute pancreatitis, other etiological factors may co-exist, such as gallstones, hypertriglyceridemia or genetic mutations, and should first be ruled out (58, 59). The standard diagnostic work-up is described in the IAP/APA guidelines and includes extensive clinical history (i.e. use of drugs, recent trauma or ERCP, family history), laboratory tests including calcium and triglycerides and transabdominal ultrasound (18). Because pancreatitis recurrence is the primary endpoint, we have chosen not to include patients with two or more potential etiologies.

In the PANDA trial design, patients with alcohol dependence, defined as an AUDIT higher than 15 (for women higher than 13), will be excluded. Since alcohol-dependent patients should be offered referral to an addiction specialist (44), it is considered unethical to not intervene when referral does not follow for alcohol-dependent patients in the control arm. Moreover, population heterogeneity becomes more pronounced if both patients with harmful drinking and alcohol dependence will be included (60).

Participating hospitals, instead of patients, are randomized as clusters between the intervention program and control program to prevent confounding and contamination. This methodology has several advantages. First, in a cluster RCT design, more patients are likely to give informed consent for data collection and to fill out questionnaires, including those less intrinsically motivated patients that would refuse participation in a traditional RCT. Thus, subjects are more likely to be an adequate reflection of the actual population of acute alcoholic pancreatitis patients, increasing external validity of study findings. Second, in a traditional RCT design, patients are more likely to proactively self-educate using the information in the patient information letter, than they would in case of a cluster randomized design. Lastly, the nature of an intervention program implicates a high risk of contamination on the clinician level, because it may prove to be difficult for a clinician, trained to execute a proactive program, to withhold some easily completed steps from the patients in the control group. Both

contamination on the clinician level and patient level may lead to an underestimation of the treatment effect. Therefore, a cluster randomized trial design is considered the preferred design for the PANDA trial. Additionally, clusters are stratified based on type of hospital (academic versus non-academic), because of expected low versus high rates of first admissions related to acute alcoholic pancreatitis.

Recurrence of acute pancreatitis, irrespective of etiology, within one year after inclusion is the primary endpoint. In the longest follow-up study of acute alcoholic pancreatitis patients, 46% developed a recurrent attack in 10 to 20 years, of whom 70% within three years (10). However, the study from Nordback et al. found a statistically significant difference in the occurrence of first relapse after 6 months between the repeated-intervention arm (2%) and the single-intervention arm (13%) (20). To assess the association between alcohol intake after the first episode and recurrence of disease, subjects are asked to fill out the AUDIT-questionnaire at four time points, at 3, 6, 9 and 12 months, after inclusion. Extending the follow-up period can lead to reduced compliance with completion of questionnaires.

A potential drawback of the PANDA trial design is that it only includes hospitals in the Netherlands, which may limit the applicability of our alcohol cessation program, primarily based on Dutch guidelines, to other countries and cultures. Additionally, our deliberate decision to not focus on concurrent nicotine use is driven by both the philosophy of treating one ''addiction'' at a time and practical feasibility considerations. Lastly, in a trial involving a rare condition such as the initial occurrence of acute alcoholic pancreatitis, patient recruitment is expected to be challenging.

CONCLUSION

The PANDA trial is a multicenter, cluster randomized superiority trial to investigate whether implementation of a structured alcohol cessation support program reduces recurrent acute pancreatitis in patients with acute alcoholic pancreatitis, as compared with current practice.

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Additional file 1. AUDIT questionnaire

Instruction: the next questions are about your use of alcoholic drinks, such as beer, wine, gin and the like in the last year. Question 2 and 3 refer to the glasses that are usually used to drink. These are called standard drinks. A bottle of beer is a little bit more: 1.2 standard drinks, and half a liter of beer is 2 standard drinks. A whole bottle of wine is 8 standard drinks. Your answers will be handled confidentially, so please be honest. Circle the text in the panel that matches your answer to the question the most.

Questions:	**0**	**1**	**2**	**3**	**4**
How often do you have a drink containing alcohol?	Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week
How many standard drinks containing alcohol do you have on a typical day when drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more
How often do you have six or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
During the past year, how often have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
During the past year, how often have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
During the past year, how often have you needed a drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
During the past year, how often have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
During the past year, have you been unable to remember what happened the night before because you had been drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
Have you or someone else been injured as a result of your drinking?	No		Yes, but not in the past year		Yes, during the past year
Has a relative or friend, doctor or other health worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the past year		Yes, during the past year

Additional file 2. Definitions of etiology

Alcoholic pancreatitis: pancreatitis caused by an excess intake of alcohol, diagnosed when no other etiology is demonstrated by standard work-up and the patient has an AUDIT score > 7.

Biliary pancreatitis: pancreatitis caused by biliary stones, microlithiasis or sludge, diagnosed when one of the following features is present on transabdominal ultrasound:

a. Gallstones, microlithiasis and/or biliary sludge, either in the gall bladder, ductus cysticus, intrahepatic bile ducts or in the common bile duct, and/or
b. A dilated common bile duct of more than eight mm in patients 75 years old or younger or more than ten mm in patients older than 75 years at diagnosis of acute pancreatitis

Chronic pancreatitis: a chronic inflammation of the pancreatic parenchyma, defined as typical clinical history of chronic pancreatitis (such as recurrent pancreatitis or abdominal pain, except for primary painless pancreatitis) and one or more of the following:

1. Pancreatic calcifications
2. Moderate or marked ductal lesions, defined as two or more of the following abnormal features on transabdominal ultrasound, CT or MRI/MRCP, according to the Cambridge classification:

a. Main pancreatic duct abnormalities, either enlargement or increased echogenicity of the duct wall (mandatory)
b. Pancreatic enlargement
c. Cavities
d. Duct irregularities including intraductal fillings defects, calculi or duct obstruction
e. Focal acute pancreatitis
f. Parenchymal heterogeneity
g. Irregularities of pancreatic head or body contour

3. Moderate or marked ductal lesions, defined as five or more of the following abnormal features on endoscopic ultrasound:

a. Enlarged gland size
b. Cysts
c. Echo-poor lesions (focal areas of reduced echogenicity)
d. Echo-rich lesions (more than three mm in diameter)
e. Accentuation of lobular pattern (e.g., echo-poor normal parenchyma surrounded by hyperechoic strands)
f. Increased duct wall echogenicity

g. Irregularity of the main pancreatic duct (e.g., with narrowing of the duct)
h. Dilation of the main pancreatic duct
i. Visible side branches (e.g., with dilation)
j. Calcification (of the pancreatic duct)
4. Marked and persistent exocrine insufficiency defined as pancreatic steatorrhea markedly reduced by enzyme supplementation
5. Typical histology of an adequate histological specimen

Note: during initial diagnostic work-up during admission 'marked and persistent exocrine insufficiency' cannot be evaluated properly. Therefore, this part of the definition of chronic pancreatitis will not be applicable during standard work-up. Obtaining histology is also not part of standard work-up.

Cystic fibrosis related pancreatitis: cystic fibrosis is an autosomal recessive disorder caused by a mutation in the CFTR gene, resulting in defective chloride channels in epithelial cells, diagnosed by either a concentration in sweat of chloride greater than 60 mmol/L on repeated analysis, confirmation of a CFTR gene mutation, or both. Cystic fibrosis related pancreatitis is caused by defective ductular and acinar pancreatic secretion, diagnosed when a patient with a history of cystic fibrosis presents with an acute pancreatitis in the absence of another origin.

Familial pancreatitis: acute pancreatitis from any cause that occurs in a family with an incidence that is greater than would be expected by chance alone, given the size of the family and the standardized incidence of pancreatitis within the Dutch population, defined as acute pancreatitis in patients who have two or more direct blood-related family members (parents, children or siblings) who have had an episode of acute pancreatitis.

Hereditary pancreatitis: otherwise unexplained pancreatitis in an individual from a family in which the pancreatitis phenotype appears to be inherited through a disease-causing gene mutation expressed in an autosomal dominant pattern, defined as pancreatitis in patients with a known mutation in the PRSS1 gene, the SPINK1 gene, the CFTR gene, the CTRC gene, the CLDN2 gene or the CPA1 gene, or if the patient has a direct family member (parents, children, siblings) with one or more of the above mentioned mutations and has at least one direct family member who has had an episode of acute pancreatitis or has chronic pancreatitis.

Hypercalcemic pancreatitis: acute pancreatitis caused by hypercalcemia and diagnosed when no signs of a biliary pancreatitis are found in standard work-up and the patient

has a blood serum calcium level of at least 12 mg/dl or 3 mmol/l, corrected for the serum albumin level, as first measured during admission.

Hypertriglyceridemic pancreatitis: acute pancreatitis based on hypertriglyceridemia and diagnosed if a biliary etiology is not demonstrated by standard work-up and the patient has a blood serum triglyceride level of at least 1000 mg/dl (or 11.2 mmol/l) under fasting conditions, as first measured during admission.

Idiopathic acute pancreatitis is considered to be present if no etiology is found in standard work-up (see all definitions).

Medication associated pancreatitis: acute pancreatitis is considered when the patient uses one or multiple drug(s) listed in the table below, the drug has been started or increased in dosage within a reasonable temporal sequence, in principle 1 month before the onset of the pancreatitis, and has a positive dechallenge (a drug reaction that is confirmed by stopping the drug.

Drugs associated with acute pancreatitis
Definite association: Acetaminophen, asparaginase, azathioprine, bortezomib, capecitabine, carbamazepine, cimetidine, cisplatin, cytarabine, didanosine, enalapril, erythromycin, oestrogens, furosemide, hydrochlorothiazide, interferon alfa, itraconazole, lamivudine, mercaptopurine, mesalazine, olsalazine, methyldopa, metronidazole, octreotide, olanzapine, opiates, oxyphenbutazone, pentamidine, pentavalent antimony compounds, phenformin, simvastatin, steroids, sulfasalazine, co-trimoxazole

Pancreas divisum: a congenital malformation of the main pancreatic duct (Wirsung's duct) with two separate ducts (a separate ventral duct of Wirsung and a dorsal duct of Santorini) as opposed to one main duct (of Wirsung).

Post-ERCP pancreatitis: pancreatitis caused by mechanical injury from instrumentation and hydrostatic injury from contrast injection during ERCP, diagnosed if a patient develops a pancreatitis within 24 hours of an ERCP without indications of another origin.

Postoperative pancreatitis: pancreatitis caused by perioperative hypoperfusion of the pancreas, diagnosed if a patient develops a pancreatitis within 24 hours of abdominal surgery in the absence of indications for another origin.

Posttraumatic pancreatitis: pancreatitis caused by pancreatic injury due to trauma to the abdomen, diagnosed when the patient describes a typical blunt trauma to the upper abdomen and pancreatic trauma is visible on imaging.

Additional file 3. Definition of standard diagnostic work-up

1. A detailed personal history, including questions on:
    a. Known gallstone disease
    b. Alcohol use
    c. Recent start of or changes in use of drugs associated with acute pancreatitis
    d. Known hyperlipidemia
    e. Known cystic fibrosis
    f. Recent major abdominal trauma
    g. Recent abdominal surgery
    h. Recent ERCP
2. A detailed family history, including questions on:
    a. Familial pancreatitis
    b. Hereditary pancreatitis
3. Laboratory tests, including:
    a. Blood serum triglycerides level
    b. Blood serum calcium level, corrected for the serum albumin level
    c. Blood serum liver enzymes level on admission
4. Imaging via transabdominal ultrasound

Additional file 4. SOP intervention program

Medical phase (treating physician)

- o If applicable, start or continue vitamin suppletion
- o If applicable, start or continue treatment of withdrawal symptoms

Education phase (treating physician)

- o Provide the patient with information about the relationship between pancreatitis and alcohol use by 1) make connection 2) ask permission 3) speak in the third person and 4) connect again. For example:

    - Make connection: *what do you already know about acute pancreatitis?*
    - Ask permission: *may I tell you something about this disease?*
    - Speak in third person: *many people who develop acute pancreatitis have an alcoholic cause. Previous research show that 25% of these patients will have recurrent attacks, but that this rate can be reduced to near 0% when someone managed to stop drinking alcohol. For this reason, we advise to stop drinking alcohol completely in all patients who have suffered from acute pancreatitis.*
    - Connect again: *what is your perspective on this?*

- o Make clear that the primary care physician can offer supportive treatment regarding alcohol use and encourage the patient to visit primary care
- o In case the patient is not motivated to seek for further treatment in primary care, refer to e-mental health (www.thuisarts.nl/alcohol) or support groups (Alcoholics Anonymous)
- o Provide the brochure '*Everything you need to know about alcohol*' from the Trimbos Institute

Motivation phase (by psychosocial professional)

- o Ask open-ended questions (without judging) about patient's alcohol use and evaluate whether the patient use change talk (statements about change) or sustain talk (statements about sustaining drinking behavior without change.
- o Evoke change talk with the patient. Ask about the disadvantages of continuing alcohol use and the advantages of changing alcohol use. Examples of evocative questions: *If you were successful in making this change, what would be different? What are worse things that might happen if you do not make this change?*
- o Identify patient's motivation to change and confidence in ability to change. Ask scale questions (1-10) or other evocative questions: *On a scale from zero to ten, how important is it to you to change? Why are you at X and not a lower number? On a scale from zero to ten, how confident are you that you could change? Why are you at X and not a lower number? Why do you think it is important to change?*

- Explore patient's individual treatment goals, such as cessation or reduction of alcohol use or change in drinking habits: *if you decide to change, what would you like to achieve? What changes were you thinking about making? When have you made a significant change in your life before? What strengths do you have that would help you to achieve a change?*
- Empower the patient
- Motivate the patient to seek for further treatment, for example in the setting of primary care

Discharge phase (treating physician)

- Direct contact with general practitioner regarding imminent discharge
- Share summary of the reason of hospitalization, the medical treatment provided, the patient's problematic behavior of drinking, his or her motivation to change and eventually, treatment goals to achieve the desired change
- Advise the general practitioner to contact the patient after discharge

Home phase (study coordinator)

- Send a letter with information about this study to the general practitioner and promote awareness and adherence of their own guidelines on Problematic alcohol use

Additional file 5. Modified AUDIT questionnaire

*Instruction***:** the next questions are about your use of alcoholic drinks, such as beer, wine, gin and the like since your admission for acute pancreatitis. Question 2 and 3 refer to the glasses that are usually used to drink. These are called standard drinks. A bottle of beer is a little bit more: 1.2 standard drinks, and half a liter of beer is 2 standard drinks. A whole bottle of wine is 8 standard drinks. Your answers will be handled confidentially, so please be honest. Circle the text in the panel that matches your answer to the question the most.

Questions:	**0**	**1**	**2**	**3**	**4**
How often do you have a drink containing alcohol?	Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week
How many standard drinks containing alcohol do you have on a typical day when drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more
How often do you have six or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
How often have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
How often have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
How often have you needed a drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
How often have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
Have you been unable to remember what happened the night before because you had been drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
Have you or someone else been injured as a result of your drinking?	No		Yes, but not since my admission for acute pancreatitis		Yes, also since my admission for acute pancreatitis
Has a relative or friend, doctor or other health worker been concerned about your drinking or suggested you cut down?	No		Yes, but not since my admission for acute pancreatitis		Yes, also since my admission for acute pancreatitis

Additional file 6. Participating Dutch centers

1. Admiraal de Ruyter Hospital, Goes
2. Alrijne Hospital, Leiderdorp
3. Amsterdam University Medical Centers, Amsterdam
4. Bravis Hospital, Roosendaal
5. Canisius Wilhelmina Hospital, Nijmegen
6. Catharina Hospital, Eindhoven
7. Deventer Hospital, Deventer
8. Dijklander Hospital, Hoorn
9. Erasmus MC, Rotterdam
10. Flevo Hospital, Almere
11. Franciscus Gasthuis and Vlietland, Rotterdam
12. Gelre Hospitals, Apeldoorn
13. Haga Hospital, The Hague
14. Hospital Gelderse Vallei, Ede
15. Ikazia Hospital, Rotterdam
16. Isala, Zwolle
17. Leiden University Medical Center
18. Maasstad Hospital, Rotterdam
19. Meander MC, Amersfoort
20. Medical Center Leeuwarden, Leeuwarden
21. Medical Spectrum Twente, Enschede
22. Maastricht UMC+, Maastricht
23. NoordWest Ziekenhuisgroep, Alkmaar
24. OLVG, Amsterdam
25. Radboud University Medical Center, Nijmegen
26. Reinier de Graaf Gasthuis, Delft
27. Sint Antonius Hospital, Nieuwegein
28. Spaarne Gasthuis, Hoofddorp
29. TerGooi, Hilversum
30. Treant Zorggroep, Emmen
31. University Medical Center Utrecht, Utrecht
32. Ziekenhuisgroep Twente, Hengelo
33. Zuyderland MC, Sittard

CHAPTER 10

General discussion and future perspectives

GENERAL DISCUSSION

Acute pancreatitis is a major burden in the Western world. As its incidence has increased significantly over the years and continues to rise, the incidence of both necrotizing pancreatitis and recurrent acute pancreatitis is also expected to increase. Necrotizing pancreatitis carries the risk of complications such as infected necrosis and splanchnic vein thrombosis, whereas each recurrent attack has the potential for the development of necrotizing pancreatitis. To break this vicious cycle, it is of paramount importance to optimize the clinical management of acute pancreatitis. The aim of the studies described in this thesis was to improve strategies *'from treatment to prevention'*.

PART I – TREATMENT OF INFECTED NECROTIZING PANCREATITIS

After antibiotics, the next indicated step in the treatment of infected necrotizing pancreatitis is catheter drainage (1). The goal is to eradicate the source of infection, but the best time to do so has long been debated (2). The POINTER trial recently showed that delayed drainage offers short-term benefits compared with immediate drainage, but its effect on long-term clinical outcomes remained uncertain.

As discussed in **Chapter 2**, the long-term follow-up results of the POINTER trial showed that the following benefits of delayed drainage persisted after more than 4 years of follow-up. First, fewer pancreatic interventions were performed in patients treated with a delayed drainage strategy. Second, the need for intervention was avoided in more than one-third of these patients. Finally, the delayed drainage strategy was not associated with increased with long-term mortality, morbidity, or complications such as recurrent pancreatitis, pancreatic insufficiency, and impaired quality of life. These results were consistent with a recent meta-analysis that included the original POINTER trial and six other studies (3). However, all but one of these studies were retrospective and lacked long-term follow-up (4-9). Nevertheless, we show that a follow-up period of ~2 years seems appropriate for future studies. All POINTER participants had their first drainage procedure, if needed, within 22 months after randomization. Although this is the first long-term cohort study based on prospective randomized data, our results should be considered with some limitations. The majority of patients did not have organ failure at randomization. Some patients were excluded because the treating physician decided that delayed drainage was not feasible. This may have led to an overestimation of the treatment effect of the delayed drainage strategy. Preliminary results from a pilot study showed a beneficial trend for immediate drainage when initiated on the basis of persistent organ failure (10). A full

randomized controlled trial is needed to provide definitive results. Furthermore, the indication for (additional) interventions was not standardized. In the Netherlands, however, guidance on interventions is generally provided by our expert panel system (11). The results of this study provide additional guidance on when to intervene. The starting point is an initial antibiotic-only approach, where the effect of antibiotics can be safely awaited if there is subsequent clinical improvement. This approach offers the opportunity to avoid and reduce the number of invasive procedures.

Future perspectives

An important direction for future research in infected necrotizing pancreatitis is the optimization of antibiotic treatment. Especially as we have shown that treatment is moving towards an even more conservative approach with antibiotics. Currently, there are concerns about the overuse and misuse of antibiotics in patients with (infected) necrotizing pancreatitis. Overuse because antibiotics are often started early in the course of the disease and/or without evidence of infection (12-14). In addition, antibiotics, often broad-spectrum, are continued for long periods of time because the duration of treatment has not yet been standardized (12). And misuse, because microbiological cultures are not always consistent with antibiotic use or are not obtained (12). Routine fine needle aspiration has the potential to overcome the latter (15). Another emerging strategy is antibiotic stewardship programs. These programs address the optimal type, dose, and duration of antibiotic treatment and have been shown to reduce both length of hospital stay and antibiotic resistance. (16-18) The upcoming PIANO trial within the Dutch Pancreatitis Study Group (DPSG) will provide useful data on the implementation of an antibiotic stewardship, including recommendations on when to obtain cultures, in our study population.

In an ideal world, improved antibiotic therapies would eliminate the need for invasive procedures. However, we are not there just yet. The endoscopic step-up approach is now the preferred method (19), so innovation in this area is of great value. In addition to conventional endoscopic drainage and necrosectomy techniques, there are several innovations worth exploring. Placement of a nasocystic tube alongside the transmural stent(s) may be useful to facilitate continuous irrigation of necrotic debris (20). Such a tube may also allow irrigation of necrotic collections with hydrogen peroxide or antibiotics. Hydrogen peroxide may aid in the removal of necrotic debris through the release of oxygen (21, 22). Local administration of antibiotics has the advantage of delivering high concentrations directly to the site of infection (23, 24). The EndoRotor, an automated tissue resection device, could potentially reduce the duration of necrosectomy procedures (25, 26). The latter innovation is now being evaluated in the randomized RESOlVE trial of the DPSG.

As this thesis goes '*from treatment to prevention*', drawing attention to strategies aimed at preventing the risk of a severe disease course is key. Intravenous omega-3 fatty acids ('fish oil') and oral tributyrin (a butyrate prodrug) are promising early-phase agents. Omega-3 fatty acids are known inducers of anti-inflammatory cytokines (27), and may therefore reduce the systemic inflammatory response underlying necrotizing pancreatitis (28, 29). The prophylactic potential of butyrate, a short-chain fatty acid produced by the gut microbiota itself (30), may target bacterial translocation from the gut (31), which is thought to be responsible for the infection of necrosis (32). The hypothesis that both strategies improve clinical outcomes is currently being tested in the DPSG's Phase III PLANCTON trial and the Phase IIa PARROT trial.

PART II – SPLANCHNIC VEIN THROMBOSIS IN ACUTE PANCREATITIS

Therapeutic anticoagulation for splanchnic vein thrombosis aims to prevent bowel ischemia and promote vessel recanalization. Recanalization, in turn, helps to reduce splanchnic hypertension and the risk of bleeding (33). However, its current role in acute pancreatitis remained unclear (34, 35).

To address this, we conducted a systematic review and meta-analysis of the available literature. In **Chapter 3,** we analyzed and presented the combined results of seven retrospective cohort studies involving 233 patients with acute pancreatitis and splanchnic vein thrombosis. The most commonly affected vein was the splenic vein, and approximately half of the patients received anticoagulation. Pooled analyses showed no association between anticoagulation and improved clinical and radiological outcomes. The main limitation of this systematic review was the small number of available studies (36-42), and the low quality of the included studies, as no randomized or prospective studies were identified. Therefore, the potential influence of the patient's clinical context on anticoagulant decisions, known as confounding by indication, cannot be excluded. This means that no recommendation can yet be made regarding the use of anticoagulation for splanchnic vein thrombosis in acute pancreatitis. Compared to other non-pancreatitis cohorts (33), we observed a relatively low proportion of treated patients. In addition, the use of anticoagulation varied widely between different thrombus sites and between the seven studies (20-79%).

To further study the current practice of anticoagulation in this clinical context in the Netherlands, a survey and case vignette study of 93 Dutch pancreatologists is described in **Chapter 4.** The responding pancreatologists agreed on anticoagulant therapy for splanchnic vein thrombosis. Preferred indications were acute portal vein thrombosis

and thrombus progression, regardless of the presence of (suspected) infected necrosis. The majority believed that anticoagulation improved clinical outcomes. Although this is the first survey on this topic and the response rate was relatively high (67%), it is important to note that we did not use the Delphi technique to reach consensus. Therefore, it remains unknown whether these shared opinions are valid and reflect practice in other countries. It was also not possible to evaluate the treatment decision for each possible scenario. The clinical course of both splanchnic vein thrombosis and acute pancreatitis is highly variable. I believe this is exactly the reason why it is difficult to conduct high-quality, comparable studies. However, given the results of both the meta-analysis and the survey, we could hypothesize that not all splanchnic vein thromboses are treated in current practice. Perhaps this may not be necessary. In fact, the only available practice guideline on the management of splanchnic vein thrombosis in acute pancreatitis, written by the Chinese Pancreas Study Group, recommends anticoagulation specifically for thrombosis extending to the mesenteric vein and with clinical signs of bowel ischemia (43). However, the level of evidence for this recommendation is weak.

To better understand the potential role of anticoagulation, we performed a post-hoc analysis of a prospective cohort of 432 patients with necrotizing pancreatitis. As detailed in **Chapter 5**, bowel ischemia emerged as a rare but serious complication in patients with splanchnic vein thrombosis, leading to death in all cases. This indeed speaks to the severity of mesenteric vein thrombosis. We also found an association between splanchnic vein thrombosis and admission to the intensive care. The results were similar after adequate adjustment for disease severity, which was done for the first time in this study. Given this, future research should continue to focus on improving therapeutic strategies. Other relevant findings were that splanchnic vein thrombosis was detected in nearly one in four patients after a median of 4 days, while spontaneous recanalization occurred in more than half of the patients within a median of 3 weeks. Parenchymal necrosis, with left, central, or subtotal necrosis being the pattern with the highest risk, and younger age were identified as independent risk factors. These findings may have several clinical implications. First, a comprehensive evaluation of splanchnic vein thrombosis on an early computed tomography scan, often performed three to four days after onset to assess disease severity, seems to be important. Early treatment with therapeutic anticoagulation could then be considered, which has been associated with higher recanalization rates (44). Second, timely drainage of (infected) necrotic collections to prevent or treat splanchnic vein thrombosis does not seem to have a place in management. This is because both thrombus formation and recanalization occur at an early stage, in the absence of modifiable risk factors, and when collections are not yet walled off (45). Unfortunately, as with the other observational

studies, our data on anticoagulant therapy were limited by potential confounding. Therefore, this study does not add further evidence to the previous meta-analysis.

Future perspectives

Our assessment of splanchnic vein thrombosis has confirmed that the evidence for the efficacy and safety of therapeutic anticoagulation in the context of acute pancreatitis is inconclusive. Further high-quality studies are thus required. A tailored approach based on the site of thrombosis is now of particular interest and should be incorporated in these studies. Such an approach may become an alternative to the universal recommendations outlined in current thrombotic guidelines (46-49). Splanchnic vein thrombosis involves different veins originating from different organs and has different clinical consequences (50, 51). Therefore, the risk-benefit ratio may differ depending on the site of thrombosis.

A randomized controlled trial is considered the gold standard for evaluating the effectiveness of a treatment (52). However, in the case of pancreatitis-related splanchnic vein thrombosis, this may not be feasible. Especially when each thrombus site is evaluated as a separate entity. Approximately 20% of patients with acute pancreatitis progress to necrotizing pancreatitis (53). Splanchnic vein thrombosis was found in one-fifth of these patients, with involvement of the splenic vein, portal vein, and superior mesenteric vein seen in ~60%-50%-40% of cases (Chapter 5). A possible strategy to overcome the sample size problem is to extend the inclusion criteria to all provoked splanchnic vein thrombosis based on transient and local risk factors such as other abdominal infections.

Although the ultimate goal is to achieve the highest level of evidence, this does not mean that lower levels of evidence cannot be a way forward. Testing a selective anticoagulation policy in cohort studies is an interesting research method. A recent single-center retrospective study evaluated their current policy of reserving anticoagulation for all portal vein/superior mesenteric vein thrombosis and only for progressive splenic vein thrombosis, and showed improved outcomes (54). Future prospective studies are needed to provide a more detailed description of patient selection, as well as predefined selection of type and duration of anticoagulation, and follow-up. Taking into account the risk of complications, this should preferably be done with a control group not receiving anticoagulation. A multicenter study design would help to confirm the applicability to other clinical settings.

PART III – PREVENTION OF RECURRENT ACUTE PANCREATITIS

Identifying patients at risk for disease progression after a first episode of acute pancreatitis could facilitate preventive treatment strategies. Recurrent acute pancreatitis is often the first event to follow and was therefore the main focus of this part.

Chapter 6 presented the results of the longest clinical follow-up study to date of 1,184 patients with acute pancreatitis, therefore providing an accurate estimate of progression rates. Nearly one in four patients developed recurrent acute pancreatitis after their first episode. These rates were three and two times higher for alcoholic and idiopathic etiologies, respectively, than for biliary etiology. In the latter group, ERCP and cholecystectomy within 3 months after the onset of acute pancreatitis were found to be independent preventive factors. However, they were performed in less than one-third and two-third of patients, respectively. In addition to non-biliary etiologies, recurrent pancreatitis itself was an independent risk factor for chronic pancreatitis, and so was smoking. The association between acute pancreatitis and pancreatic cancer could not be properly studied because only a small subset of patients (n=14) was diagnosed with pancreatic cancer. Of these, most were diagnosed within 2 years after their presentation with idiopathic pancreatitis. This suggests an initial misdiagnosis in the first place (55). Longitudinal data on smoking and alcohol consumption were also lacking. The number of patients who completed the follow-up questionnaire on these behaviors was low. Despite these limitations, this study is clinically relevant because we have shown in which patients (and when) disease progression occurs. This can help inform patients about their expected prognosis. The risk factors identified provide guidance for improving preventive strategies such as lifestyle counseling, timely cholecystectomy, and close surveillance.

Chapter 7 described the results of the first study of the incidence of gallstones and their association with recurrent acute pancreatitis in patients with acute alcoholic pancreatitis, which was diagnosed at the discretion of the treating physician. Gallstones were present in nearly one in five patients. The recurrence rate was significantly higher in patients with gallstones who remained untreated than in those without gallstones or who underwent cholecystectomy. These results clearly indicate that a proportion of these patients do have an underlying biliary cause and that appropriate treatment can prevent recurrence of pancreatitis. As this is the first study on this topic, we were not able to make a head-to-head comparison. Other clinically relevant findings were that the evaluation of gallstones according to current guidelines and the treatment of gallstones were not performed consistently (1). So there is a lot of room for improvement. An important limitation is the lack of data on alcohol abstinence in

the recurrence-free group. There was no prospective analysis of alcohol or standard follow-up protocol. However, since more patients with gallstones were abstinent at the time of recurrence, it can be concluded that this did not affect our primary outcome. The total number of patients who achieved alcohol abstinence was, however, low. In addition, the recurrence rate after cholecystectomy was still high, which supports the need for alcohol cessation support treatment in addition to cholecystectomy.

Chapter 8 highlighted the lack of a routine management strategy in the Netherlands regarding alcohol cessation support for patients with acute alcoholic pancreatitis. This first national survey, with a response rate of 100%, showed that motivational interventions in the hospital setting and appropriate discharge planning were often not provided. As with all studies, results should be interpreted with several limitations. Local investigators who are involved in studies of the DPSG completed the survey on behalf of their gastroenterology department, which may have introduced recall bias. Also, the role of psychiatrists in supportive care was not included in the survey questions, which in retrospect was an omission. Nevertheless, standardized treatment protocols were not available in all but one of the departments surveyed. This suggests that current guidelines for problematic alcohol use are not well implemented or that clinicians are unaware of their recommendations (56-58). Either way, the findings highlight the need for improvements in the management of acute alcoholic pancreatitis.

The PANDA trial, a multicenter cluster randomized controlled trial whose protocol is presented in **Chapter 9**, was designed to compare a structured alcohol cessation support program with the current practice in patients with a first episode of acute alcoholic pancreatitis. The hypothesis is that additional efforts to reduce or stop alcohol consumption through the implementation of a structured program, including an in-hospital motivational intervention, will prevent recurrence of pancreatitis, reduce hospitalizations and costs, and improve patients' quality of life. The framework for this program was inspired by the findings in Chapter 8. The sample size calculation was based on the results presented in Chapter 6. Consistent with the findings in Chapter 7, acute alcoholic pancreatitis is diagnosed after a comprehensive diagnostic work-up, including transabdominal ultrasound to evaluate for gallstones. In the absence of evidence-based criteria for acute alcoholic pancreatitis, we use the Alcohol Use Disorder Identification Test (AUDIT), which is one of the best known and validated tools for screening for problematic alcohol use (59).

Future perspectives

In future research and current practice, it is important to prioritize optimal management in patients with acute alcoholic pancreatitis. These patients have the highest

incidence of recurrent acute pancreatitis. The management of alcoholic pancreatitis should involve a multidisciplinary team of clinicians, psychosocial care providers, and general practitioners. In addition to the PANDA trial, the Hungarian Pancreatic Study Group has initiated a randomized controlled trial (REAPPEAR) to evaluate whether a brief intervention program reduces the risk of recurrence in acute alcoholic pancreatitis (60). A trial that we can only encourage. This trial will also address smoking, an addiction that often goes hand in hand with problematic alcohol use (61). Smoking is an independent risk factor for recurrent acute pancreatitis, and even more so for chronic pancreatitis (62, 63). A combination of problematic alcohol use and smoking has been shown to have the highest cumulative risk for chronic pancreatitis (62). The results of both the PANDA and REAPPEAR trial will hopefully provide answers about the effectiveness of alcohol and smoking cessation programs and further guidance for clinical practice. In addition to my enthusiasm for these studies, I believe we should also look at the problem of alcohol from another angle. The normalization or social acceptance of alcohol use. Awareness of its harmful effects is currently lacking and should be a top priority (64). Other goals for the year 2040 are outlined in the National Prevention Agreement (65). These include measures to make alcohol less accessible and more expensive, and to regulate alcohol advertising.

With regard to idiopathic acute pancreatitis, the second etiology at risk for recurrent pancreatitis, we have recently made progress with the results of the PICUS study (66). Routine use of endoscopic ultrasound after a first episode of idiopathic acute pancreatitis resulted in lower recurrence rates by identifying the underlying etiology one-third of patients, and should be incorporated into current practice. The question now is how to improve outcomes in patients with a negative endoscopic ultrasound. The efficacy of cholecystectomy versus a conservative approach in these patients is currently being evaluated in the PICUS-2 trial. As shown, improving adherence to guidelines for the management of biliary etiology is another important issue. The evidence regarding the timing of cholecystectomy in the subset of patients with necrotizing pancreatitis requires further investigation (67). In a recent but retrospective study, the optimal timing was within 8 weeks of discharge in the absence of peripancreatic collections (68). For the remaining patients with mild biliary acute pancreatitis, there is strong evidence for the benefit of same-admission cholecystectomy (69). In my opinion, this should also be done in patients with a history of excessive alcohol consumption.

CONCLUSIONS

Clinical research on the management of acute pancreatitis was the focus of my thesis. Various treatment strategies were evaluated *'from treatment to prevention'*. Many op-

portunities to improve clinical practice and promising areas for future research were identified. The mission of the Dutch Pancreatitis Study Group to improve clinical outcomes for all patients with acute pancreatitis remains fundamental and will be continued.

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Appendices

NEDERLANDSE SAMENVATTING

De pancreas, ook wel bekend als de alvleesklier, is een orgaan in de buik dat belangrijke functies heeft in de spijsvertering en het reguleren van de bloedsuikerspiegel. Acute pancreatitis is een plotselinge ontsteking die in ontwikkelde landen meestal wordt veroorzaakt door galstenen of overmatig alcoholgebruik. Het is een van de meest voorkomende aandoeningen in het maagdarmstelsel die leidt tot een spoedopname in het ziekenhuis.

In de meest ernstige gevallen van acute pancreatitis kan er necrose ('afsterven van weefsel') optreden in de pancreas of in het omliggende vetweefsel. Een zorgwekkende complicatie bij deze patiënten is een secundaire infectie van dit afgestorven weefsel. Bovendien kan necrose leiden tot de vorming van trombose in belangrijke bloedvaten in de buik. Recidiverende episodes van acute pancreatitis komen voor bij een deel van de patiënten die acute pancreatitis hebben doorgemaakt. Een belangrijke rol hierbij speelt het niet detecteren of niet behandelen van de onderliggende oorzaak.

Sinds de oprichting van de Pancreatitis Werkgroep in 2002 is de behandeling van acute pancreatitis aanzienlijk verbeterd. Desondanks is het cruciaal om de behandelingsstrategieën van acute pancreatitis en de bijbehorende complicaties '*van behandeling tot preventie*' verder te ontwikkelen. Deze noodzaak wordt onderstreept door de significante toename van de incidentie van acute pancreatitis over de jaren, een trend die naar verwachting blijft toenemen. Zoals benoemd in **Hoofdstuk** 1, worden in dit proefschrift enkele klinische studies gepresenteerd die zich richten op drie aspecten binnen acute pancreatitis: de behandeling van geïnfecteerde necrotiserende pancreatitis, splanchnische veneuze trombose in acute pancreatitis, en de preventie van recidiverende acute pancreatitis.

Deel I – Behandeling van geïnfecteerde necrotiserende pancreatitis

De voorkeursbehandeling voor geïnfecteerde necrotiserende pancreatitis is de minimaal invasieve stapsgewijze aanpak, die na antibiotica vaak start met het draineren van de geïnfecteerde necrose. Voor de publicatie van de POINTER-studie was er discussie over het ideale moment voor deze drainage, vanwege achterhaalde bewijzen uit het tijdperk van open chirurgie. De multicenter, gerandomiseerde POINTER-studie toonde aan dat uitstel van drainage leidde tot minder ingrepen in vergelijking met directe drainage, en dat meer dan een derde van deze patiënten succesvol behandeld werd met alleen antibiotica. Desondanks bleef de vraag of de follow-up periode van 6 maanden voldoende was om langetermijneffecten vast te stellen, vooral bij uitgestelde drainage. In **Hoofdstuk 2** presenteerden we de resultaten van de lange termijn follow-up studie van de POINTER-studie. Hierin werden de patiënten die aan de

oorspronkelijke studie deelnamen opnieuw geëvalueerd. De resultaten toonden aan dat 93% van de patiënten die aanvankelijk conservatief behandeld waren, ook geen drainageprocedure nodig had op de lange termijn. Ook bevestigde het dat uitstel van drainage op de lange termijn tot minder ingrepen leidde. Een andere belangrijke bevinding was dat het uitstellen of zelfs weglaten van de drainageprocedure geen verhoogd risico op lange termijn complicaties gaf vergeleken met directe drainage.

Deel II – Splanchnische veneuze trombose in acute pancreatitis

Verscheidene bloedvaten in de buurt van de pancreas, zoals de vena porta, vena splenica en vena mesenterica superior (samen splanchnische venen genoemd), zijn vatbaar voor trombosevorming tijdens episodes van acute pancreatitis. Hoewel antistollingstherapie doorgaans de standaardbehandeling is voor splanchnische veneuze trombose, ontbreken specifieke behandelrichtlijnen die zijn gebaseerd op acute pancreatitis. Er bestaat een mogelijkheid dat antistolling minder effectief is bij trombose veroorzaakt door tijdelijke ontstekingen, zoals acute pancreatitis. Bovendien kan het gebruik van antistolling bij acute pancreatitis mogelijk een verhoogd bloedingsrisico met zich meebrengen. Om deze redenen hebben we in **Hoofdstuk 3** de effectiviteit en veiligheid van therapeutische antistolling bij patiënten met acute pancreatitis en splanchnische veneuze trombose onderzocht in een systematische review en meta-analyse. Deze studie omvatte zeven retrospectieve cohortstudies met in totaal 233 patiënten, waarvan ongeveer de helft behandeld werd met antistolling. Er werd aanzienlijke variatie waargenomen in het gebruik van antistolling, zowel tussen de studies onderling als bij verschillende trombuslocaties. Patiënten die behandeld werden met antistolling, vertoonden geen verbetering in klinische en radiologische uitkomsten in vergelijking met patiënten die geen antistolling kregen. De belangrijkste conclusie was echter dat de beschikbare studies van onvoldoende kwaliteit waren om onze onderzoeksvraag te beantwoorden. Dit betekent dat er geen duidelijke behandeladviezen kunnen worden opgesteld waar clinici momenteel op kunnen bouwen.

De huidige besluitvorming rond antistollingstherapie hebben we onderzocht middels een enquête onder 93 Nederlandse pancreasspecialisten, waarvan de resultaten zijn gepresenteerd in **Hoofdstuk 4**. Uit deze enquête bleek dat de pancreasspecialisten het eens waren over het gebruik van antistollingstherapie voor splanchnische veneuze trombose, met een voorkeur voor de behandeling bij acute trombose van de vena porta en in geval van progressie van trombose. De meerderheid van de ondervraagde pancreasspecialisten was van mening dat antistolling de klinische uitkomsten kan verbeteren. Echter, nieuwe klinische studies zijn noodzakelijk om deze collectieve opinie te onderbouwen. Op basis van de resultaten van zowel de meta-analyse als de enquête lijkt het erop dat momenteel niet alle trombose in de splanchnische vaten worden

behandeld met antistolling. Dit roept een belangrijke vraag op voor toekomstig onderzoek: is een dergelijke behandeling in elk scenario noodzakelijk?

Het is ook van belang om het natuurlijke beloop en de specifieke klinische gevolgen van splanchnische veneuze trombose bij patiënten met acute pancreatitis te begrijpen. Helaas is er beperkte literatuur beschikbaar over dit onderwerp in grote studiecohorten. In **Hoofdstuk 5** hebben we de resultaten gepresenteerd van een observationele, multicenter, cohortstudie met 432 patiënten met necrotiserende pancreatitis. Bij bijna een kwart werd splanchnische veneuze trombose vastgesteld na een mediane periode van 4 dagen. Een vroege CT-scan lijkt dus belangrijk om vroegtijdige antistollingsbehandeling te kunnen overwegen. Onafhankelijke risicofactoren voor het ontwikkelen van trombose waren necrose in het pancreas weefsel, vooral in de staart, of centrale of subtotale necrose, en een jongere leeftijd van de patiënt. Meer dan de helft van de patiënten vertoonde spontane rekanalisatie, vaak al binnen 3 weken. Derhalve lijkt het niet zinvol om necrotische collecties tijdig te draineren als (preventieve) behandeling van splanchnische veneuze trombose. Darmischemie bleek een zeldzame maar ernstige complicatie te zijn die in alle gevallen tot de dood leidde, wat wijst op de ernst van trombose in de vena mesenterica superior. Daarnaast vonden we dat splanchnische veneuze trombose geassocieerd is met opname op de intensive care. Deze bevindingen benadrukken de noodzaak voor verder onderzoek om therapeutische strategieën voor splanchnische veneuze trombose in acute pancreatitis te verbeteren.

Deel III – Preventie van recidiverende acute pancreatitis

Het identificeren van patiënten die na een eerste acute pancreatitis episode risico lopen op ziekteprogressie, waarbij recidiverende acute pancreatitis vaak de eerstvolgende gebeurtenis is, is belangrijk. Door deze patiënten te herkennen, kunnen preventieve behandelstrategieën effectiever worden ingezet. In **Hoofdstuk 6** worden de resultaten van een observationele, multicenter, cohortstudie naar de incidentie van ziekteprogressie bij 1.184 patiënten na hun eerste episode van acute pancreatitis beschreven. Uit deze resultaten bleek dat bijna één op de vier patiënten opnieuw acute pancreatitis ontwikkelde. De incidentie was drie keer zo hoog bij patiënten met een alcohol gerelateerde pancreatitis en twee keer zo hoog bij patiënten met een onverklaarde oorzaak, vergeleken met patiënten met galsteen gerelateerde pancreatitis. Voor de laatste groep waren endoscopische retrograde cholangiopancreatografie (ERCP) en cholecystectomie, uitgevoerd binnen 3 maanden na het begin van de eerste pancreatitis episode, onafhankelijke beschermende factoren. Echter, ERCP werd binnen deze periode maar bij een derde van de patiënten uitgevoerd en cholecystectomie bij slechts twee derde van de patiënten. Naast een niet galsteen gerelateerde oorzaak, was ook recidiverende pancreatitis zelf een onafhankelijke risicofactor voor het ontwikkelen van chronische pancreatitis, evenals roken.

Ondanks internationale richtlijnen die adviseren om galstenen te evalueren en te behandelen bij patiënten met een acute pancreatitis, is het onbekend of deze aanbevelingen ook worden opgevolgd bij patiënten met een hoge alcoholconsumptie. Noch is het onduidelijk of het negeren van deze richtlijnen invloed heeft op het risico van deze patiënten om recidiverende acute pancreatitis te ontwikkelen. In **Hoofdstuk 7** presenteren we de resultaten van een observationele, multicenter, cohortstudie uitgevoerd bij 334 patiënten met een vermoedelijk diagnose van acute alcoholische pancreatitis, gesteld door hun behandeld arts. We vonden dat bijna één op de vijf patiënten galstenen had. De aanwezigheid van deze galstenen was significant geassocieerd met een verhoogd risico op recidiverende acute pancreatitis. We ontdekten ook dat een echografie om galstenen te detecteren niet consequent werd uitgevoerd bij de eerste ziekenhuisopname. Dit gold eveneens voor het uitvoeren van een cholecystectomie nadat galstenen waren geïdentificeerd. Cholecystectomie was geassocieerd met een lager, maar nog steeds relatief hoog, percentage van recidiverende acute pancreatitis in vergelijking met patiënten met onbehandelde galstenen. Dit benadrukt dat naast de overweging om een cholecystectomie uit te voeren, het stoppen met alcoholgebruik belangrijk is.

In **Hoofdstuk 8** werd de aandacht gevestigd op het ontbreken van een standaard strategie in Nederland voor de ondersteuning bij het stoppen met alcohol bij patienten met acute alcoholische pancreatitis. Deze nationale enquête toonde aan dat motiverende interventies in het ziekenhuis en passende ontslagbeleid zelden worden toegepast. Met uitzondering van één ziekenhuis, waren er geen uniforme behandelprotocollen beschikbaar op de ondervraagde afdelingen. Dit suggereert dat de huidige richtlijnen voor problematisch alcoholgebruik niet worden geïmplementeerd, of dat betrokken zorgverleners mogelijk niet op de hoogte zijn van deze aanbevelingen. Deze bevindingen onderstrepen de dringende behoefte aan verbeteringen in de behandeling van patiënten met acute alcoholische pancreatitis.

Een gedetailleerde beschrijving van het studieprotocol van de multicenter cluster gerandomiseerde PANDA-studie werd beschreven in **Hoofdstuk 9**. Deze studie heeft als doel te onderzoeken of de implementatie van een gestructureerd ondersteuningsprogramma voor het verminderen of stoppen van alcoholgebruik kan helpen bij voorkomen van recidiverende acute pancreatitis bij patiënten die een eerste episode van acute alcoholische pancreatitis hebben doorgemaakt, in vergelijking met de huidige standaardzorg. Naast het primaire doel kijkt de studie ook naar secundaire uitkomstmaten, waaronder de reductie of het stoppen van alcoholgebruik, het voorkomen van andere alcohol gerelateerde ziekten, mortaliteit, kwaliteit van leven, en de kosten van de zorgkost. De follow-up periode beslaat één jaar na de inclusie van de patiënten.

Deze studie is een nog lopend project waarbij 33 Nederlandse ziekenhuizen betrokken zijn.

Samenvattend heeft dit proefschrift zich gericht op klinisch onderzoek waarin verschillende behandelstrategieën '*van behandeling tot preventie*' van acute pancreatitis zijn geëvalueerd. Deze onderzoeken hebben nieuwe inzichten opgeleverd om de huidige klinische praktijk te verbeteren en hebben veelbelovende gebieden voor toekomstig onderzoek blootgelegd, zoals besproken in **Hoofdstuk 10**. De inspanningen van de Pancreatitis Werkgroep Nederland om de klinische uitkomsten voor alle patiënten met acute pancreatitis te verbeteren, blijven van cruciaal belang en zullen onverminderd worden voortgezet.

LIST OF PUBLICATIONS

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CURRICULUM VITAE

Noor Josien Sissingh was born on May 18th, 1993 in Assen, the Netherlands. She grew up in Borger together with her parents, sisters and twin brother. Her childhood consisted of playing ball games (hockey, tennis), which she continued to enjoy throughout her life. After graduating from the Athenaeum at the Esdal College in Emmen in 2011, Noor started medical school at the University of Groningen. In the following years she also worked as a triagist at the General Practitioner Emergency Center, traveled through Central America, and did an internship in tropical medicine in Suriname. After obtaining her master's degree in 2018, she moved to Amsterdam and started as a resident in Internal Medicine at the BovenIJ Hospital in Amsterdam, and continued as a resident in Gastroenterology and Hepatology at the Leiden University Medical Center in Leiden. In June 2020 Noor started her PhD trajectory at the department of Gastroenterology and Hepatology at the Leiden University Medical Center, in collaboration with the Dutch Pancreatitis Study Group, located at the St. Antonius Hospital in Nieuwegein. During her PhD trajectory she coordinated the multicenter PANDA trial under the supervision of Prof. dr. Jeanin E. van Hooft (Chapter 9). Noor also designed and conducted several clinical studies using the National Registry for Acute Pancreatitis database, which are also presented in this thesis. In March 2024 Noor started as a resident general practitioner at the Leiden University Medical Center.

DANKWOORD

Het dankwoord, vaak het meest gelezen hoofdstuk van een proefschrift, biedt een prachtige kans om iedereen die een rol heeft gespeeld in mijn promotietraject te bedanken. Een aantal van hen wil ik in het bijzonder benoemen.

Promotor Jeanin van Hooft, ondanks je drukke agenda was er altijd tijd voor wekelijks overleg en stond je deur open (ik besef maar al te goed wat een luxe dat was). Jouw praktische instelling, positiviteit en snelle feedback hebben enorm bijgedragen aan de voortgang en het plezier in mijn promotieonderzoek.

Copromotor Robert Verdonk, in ons datacenter heb je met jouw aanstekelijke enthousiasme een sfeer gecreëerd waar gezelligheid en hoogstaand pancreasonderzoek samenkomen. Daarom denk ik dat ik niet alleen voor mezelf spreek als ik je bedank voor je behulpzaamheid, toewijding en belangstelling.

Copromotor Sven Mieog, jouw directe betrokkenheid bij de trombose-studies in dit proefschrift maakt jouw rol als copromotor extra waardevol. Je kritische blik tijdens onze overleggen, altijd met een vleugje humor en oprechte interesse, heeft significant bijgedragen aan de kwaliteit van de manuscripten.

Patiënten die deelnemen aan wetenschappelijk onderzoek, in het bijzonder aan de studies van de Pancreatitis Werkgroep Nederland, bedankt! Zonder jullie bijdrage zou dit proefschrift niet tot stand hebben kunnen komen.

Leden van de **Pancreatitis Werkgroep Nederland**, het was een eer om mijn promotieonderzoek uit te voeren binnen een werkgroep met zo'n indrukwekkende reputatie. De kracht van onze werkgroep schuilt in onze nationale samenwerking, die ook essentieel is geweest voor vele hoofdstukken in mijn proefschrift. Speciale dank aan Marc Besselink (Hoofdstuk 2), Casper van Eijck (Hoofdstuk 3-5), Thomas Bollen (Hoofdstuk 5) en Hjalmar van Santvoort (Hoofdstuk 6).

PWN-collega's Devica, Lotte, Christa, Fons, Hester, Fleur, Charlotte, Hannah, Mike, Naomi, Astrid, Anne en Michiel, bedankt voor de fijne en vooral gezellige samenwerking! Ik wens jullie veel succes met alle studies en hoop dat al jullie carrièrewensen uit zullen komen. Een extra vermelding gaat uit naar Fleur en Charlotte, want jullie hebben deze tijd echt onvergetelijk gemaakt. Ik koester de herinneringen aan onze carpoolritten, dinertjes, bruiloft(en), muis-en-toetsenbord samenwerkingen en de congresreisjes, met New York als onbetwist hoogtepunt. Daarnaast gaat mijn dank uit naar Hester, zelfs vanuit San Francisco stond je altijd klaar om te helpen; naar

Devica, jouw succes met de MLDS-beurs voor de PANDA-studie was cruciaal voor dit proefschrift; en naar Lotte, vanwege jouw nauwkeurige werk waar ik in Hoofdstuk 2 van heb mogen profiteren.

LUMC-collega's Vera, Emilie, Nik, Derk, Annelotte, Richard, Roberta, Tessa, Anke, Anna, Megan, Jesse (chirurgie), Lola, Susan, Anne en Alex, waar we eerst een klein clubje waren, vermenigvuldigden we zo snel dat er een verhuizing van C4 naar H3 aan te pas moest komen. Ondanks dat ik vaak in Nieuwegein te vinden was, heb ik me altijd onderdeel van het team gevoeld. Dank voor jullie gezelschap.

Lieve **vrienden**, ik ben vooral dankbaar voor de altijd gezellige afleiding die jullie hebben geboden en blijven bieden. Jullie vriendschap betekent enorm veel voor mij. Een speciale dank gaat uit naar Florieke, die mijn paranimf wil zijn en die altijd dichtbij was voor een luisterend oor.

Mijn **familie**; pap, mam, Marlot, Karlijn, Joost, Boris en aanhang, dank jullie wel voor jullie onvoorwaardelijke steun, TC's en BOJH's. Pap en mam, het succes van ons alle vier is direct te danken aan jullie opvoeding en overstijgt een simpel bedankje. Ik bedank Joost, mijn paranimf, omdat niemand anders tijdens mijn verdediging zo'n vertrouwd gevoel zou kunnen geven als jij, naast wie ik al in de couveuse lag.

Jelle, mijn grote liefde, aan jou ben ik - zonder enige twijfel - de grootste dank verschuldigd. Je hebt urenlang naar mijn promotieverhalen geluisterd, je door onbegrijpelijke teksten over pancreatitis geworsteld en mijn presentaties eindeloos verrijkt met jouw creativiteit. Maar het allermooiste is dat je me elke dag weer verrast en aan het lachen maakt. Ik hou van je en kijk uit naar al onze avonturen samen.