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

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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 haemorrhage 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.

1. 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

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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.

2. 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).

2.1. Literature search

Guided by a librarian, PubMed, Embase, Web of Science and Cochrane library databases were searched for relevant literature published until December 7th, 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.

2.2. 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.

2.3. 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.

2.4. 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 porto-portal 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).

2.5. 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.

2.6. 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.

2.7. 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].

3. Results

3.1. Study selection and characteristics

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

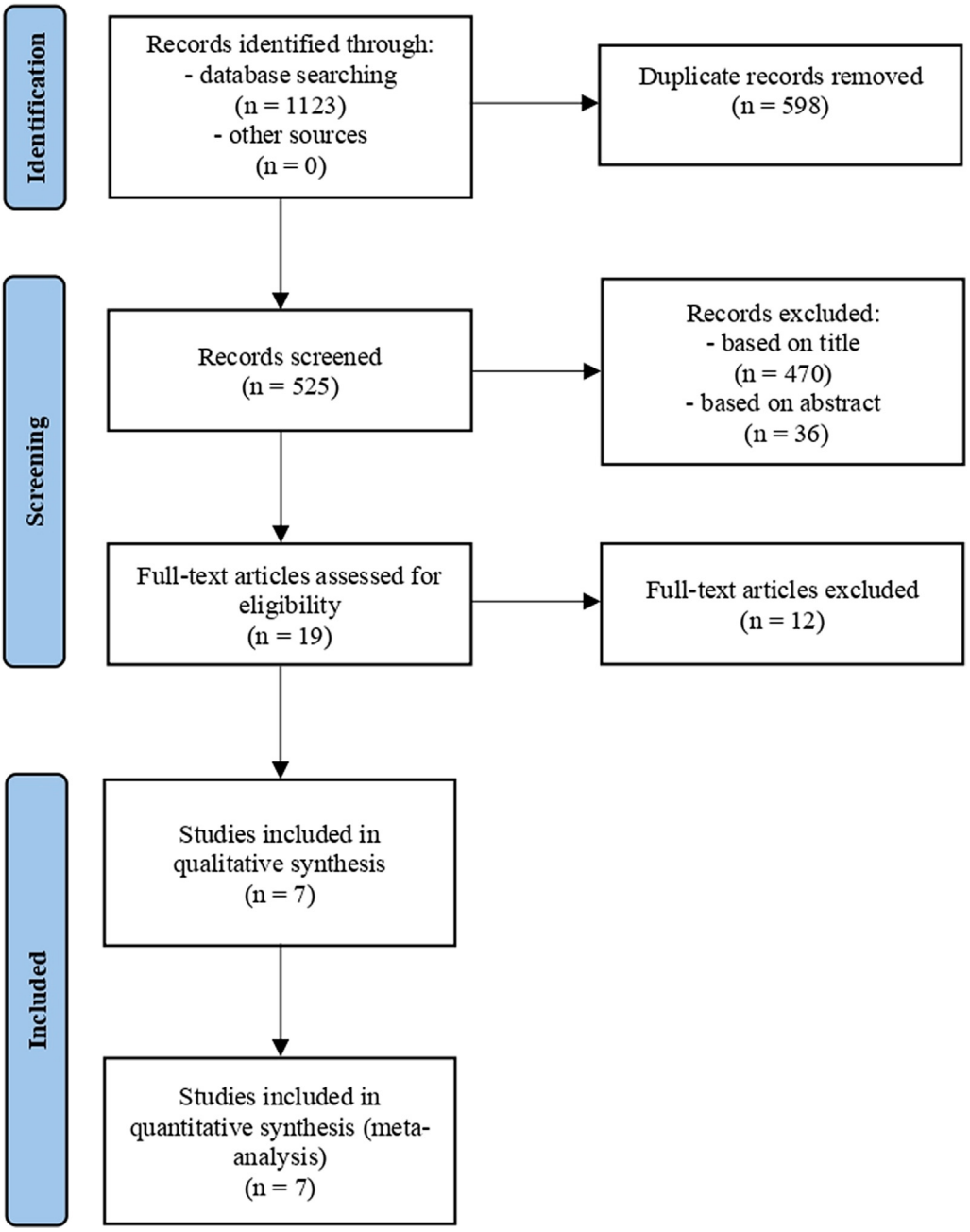

Fig. 1. PRISMA flowchart.

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%)	SpIV 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	Revised Atlanta classification	318	-	19 (6%)	SpIV 37% PV 32% SpIV + SMV 21% SpIV + PV + SMV 11%	15 (79%)	Therapeutic anticoagulation	No
Garret	2018	France	Retro	2012–2015	(moderate) severe AP	Revised Atlanta classification	148	CT findings	76 (52%)	SpIV 82%	39 (51%)	Anticoagulant therapy	No
Pagliari	2020	Italy	Retro	2015–2018	AP	Revised Atlanta classification	221	Imaging of venous complications	27 (12%)	SpIV 33% PV 4% SpIV + PV 7% SpIV + SMV 37% PV + SMV 4% PV + SMV + SpIV 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%)	SpIV 46% SpIV + PV 17% SpIV + PV + SMV 38%	12 (50%)	Heparin, subsequently warfarin	No

AP = acute pancreatitis; PV = portal vein; SpIV = splenic vein; SMV = superior mesenteric vein; SVT = splanchnic vein thrombosis; tAC = therapeutic anticoagulation.

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].

3.2. 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.

3.3. 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%) (Fig. 2A).

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

Thrombosed vessel(s)	No. (%)	Anticoagulated	
		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%

PV = portal vein; SpIV = splenic vein; SMV = superior mesenteric vein; SVT = splanchnic vein thrombosis; AC = anticoagulation.

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[b]	Low	**Moderate**
Harris	Moderate	Low	Low	Low	Low	Moderate[a]	Low	**Moderate**
Easler	Moderate	Low	Low	Low	Low	Moderate[b]	Low	**Moderate**
Toqué	Moderate	Low	Low	Low	Low	Moderate[b]	Low	**Moderate**
Garret	Moderate	Low	Low	Low	Low	Moderate[b]	Low	**Moderate**
Pagliari	Moderate	Low	Low	Low	Low	Low	Low	**Moderate**
Junare	Moderate	Low	Low	Low	Low	Moderate[b]	Low	**Moderate**

[a] Only patients having unexplained pain underwent CT at diagnosis.
[b] Follow up not stated or insufficient.

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 [21–24,26] 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. $I^2 = 0\%$) (Fig. 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. $I^2 = 2\%$) (Fig. 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. $I^2 = 0\%$) (Fig. 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.

3.4. Risk of bias across studies

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

3.5. 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.

4. 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-

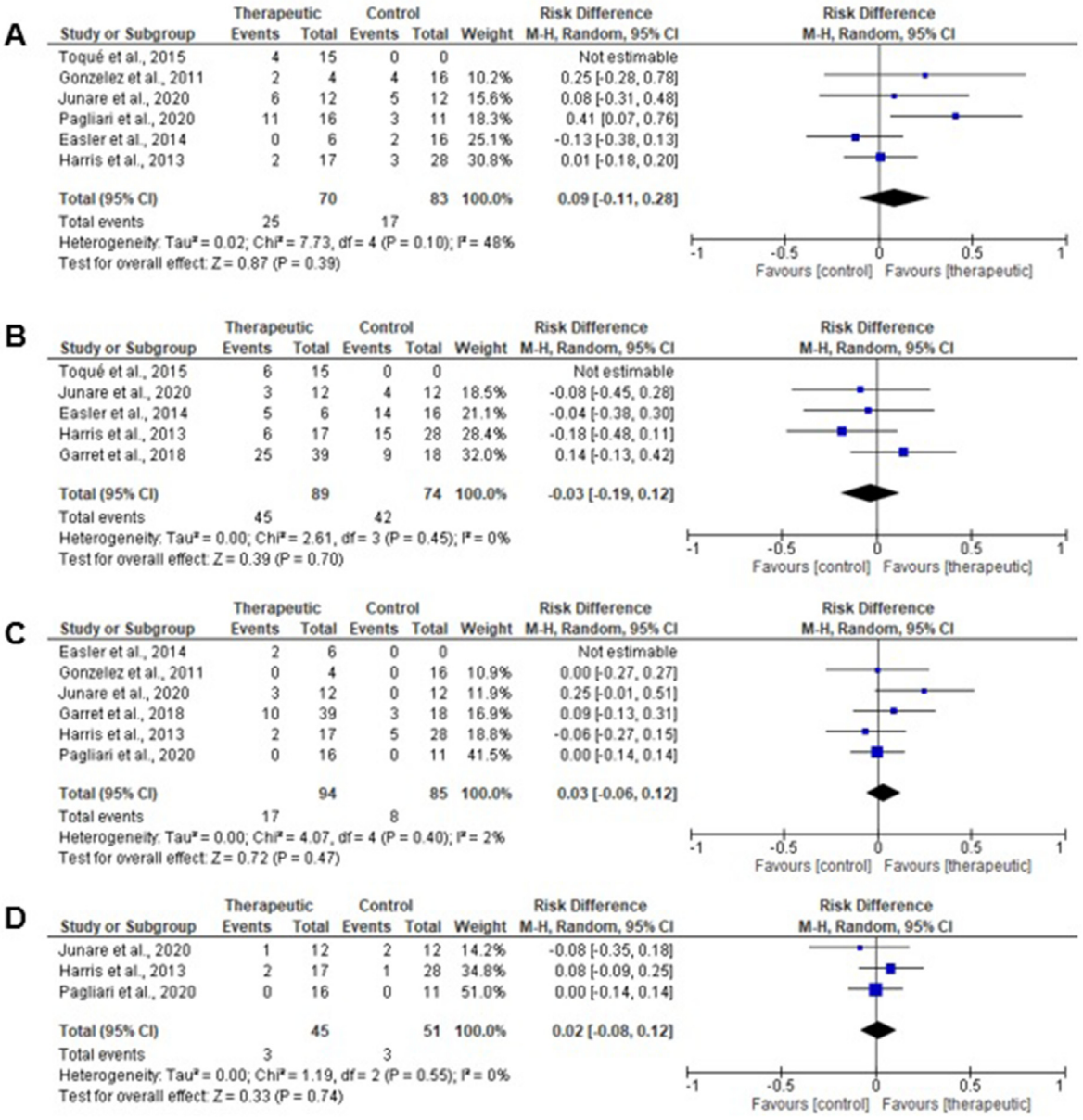

Fig. 2. Meta-analysis for recanalization (A), varices, collaterals or cavernoma (B), haemorrhage (C) and mortality (D) with a random-effects model.

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%) [16]. 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

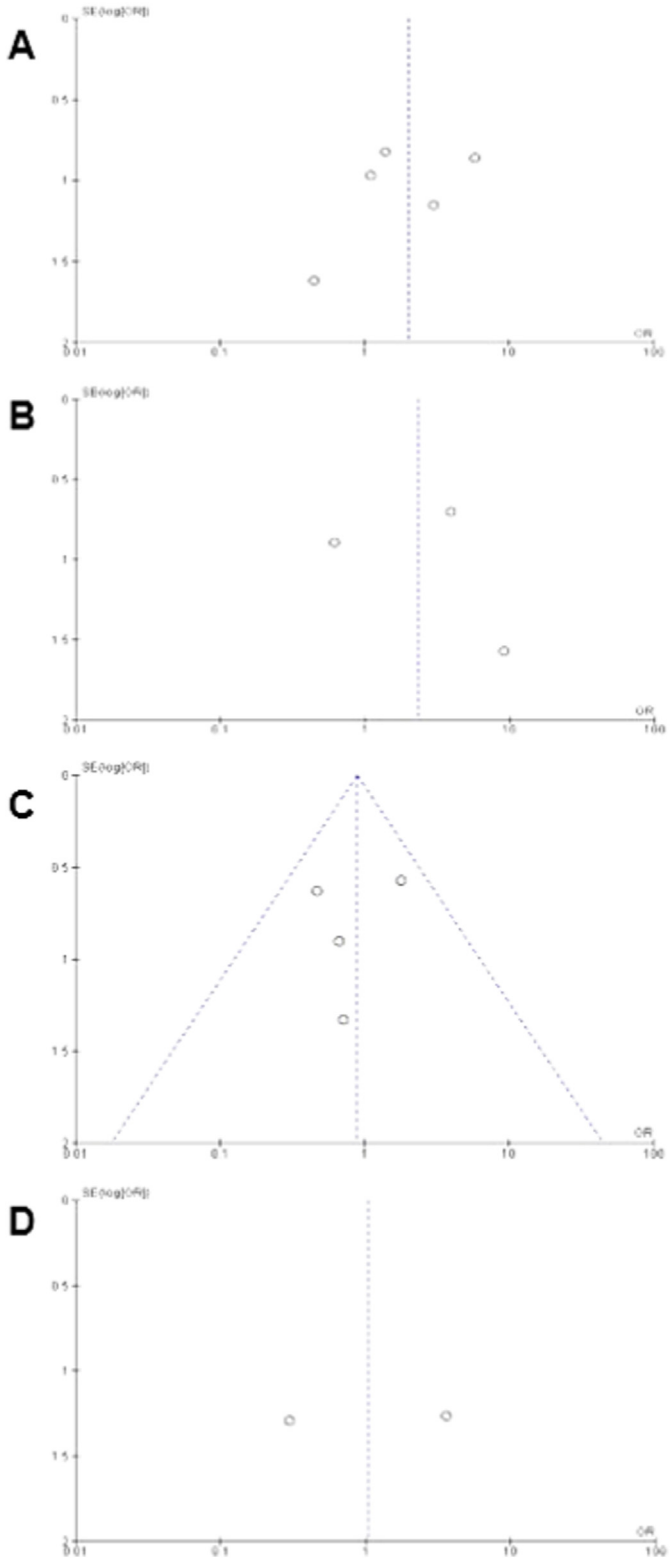

Fig. 3. Funnel plots for recanalization (A), varices, collaterals or cavernoma (B), haemorrhage (C) and mortality (D).

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%) [36]. 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 [34,37,38]. 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 and 40%) [7,39]. 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 studies 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 [40,41]. 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 [42,43]. 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-

Table 4
Quality assessment according to GRADE.

No. of studies	Design	Quality assessment				Quality of evidence
		Risk of bias	Inconsistency	Indirectness	Imprecision	
Outcome: renalization						
6	Observational studies	Serious[b]	No serious	Serious[d]	Serious[e]	Very low
Outcome: recurrent venous thromboembolism						
1	Observational studies	Serious[b]	-	No serious	No serious	Very low
Outcome: varices/collaterals/cavernoma						
5	Observational studies	Serious[b]	No serious	Serious[d]	No serious	Very low
Outcome: haemorrhage						
6	Observational studies	Serious[a]	No serious	No serious	No serious	Very low
Outcome: mortality						
3	Observational studies	Serious[c]	No serious	No serious	No serious	Very low

[a] 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.
[b] 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.
[c] 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.
[d] Downgraded one level for serious indirectness 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.
[e] 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%).

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.

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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2021.12.008.

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