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Anticoagulant therapy for splanchnic vein thrombosis: A systematic review and meta-analysis

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Abstract:
Treatment of splanchnic vein thrombosis (SVT) is challenging and evidence to guide therapeutic decisions remains scarce. The objective of this systematic review and meta-analysis was to determine the efficacy and safety of anticoagulant therapy for SVT. MEDLINE, EMBASE, and Clinicaltrial.gov were searched from inception up to December 2019 without language restrictions to include observational studies and randomized controlled trials reporting radiological or clinical outcomes in patients with SVT. Pooled proportions and risk ratios (RR) with 95% confidence intervals (CI) were calculated using a random-effects model. Of 4312 records identified by the search, 97 studies including 7969 patients were analyzed. In patients receiving anticoagulation, the rates of SVT recanalization, SVT progression, recurrent VTE, major bleeding, and overall mortality were 58% (95% CI, 51-64), 5% (95% CI, 3-7), 11% (95% CI, 8-15), 9% (95% CI, 7-12), and 11% (95% CI, 9-14), respectively. The corresponding values in patients without anticoagulation were 22% (95% CI, 15-31), 15% (95% CI, 8-27), 14% (95% CI, 9-21), 16% (95% CI, 13-20), and 25% (95% CI, 20-31). Compared with no treatment, anticoagulant therapy obtained higher recanalization (RR 2.39; 95% CI, 1.66-3.44) and lower thrombosis progression (RR 0.24; 95% CI, 0.13-0.42), major bleeding (RR 0.73; 95% CI, 0.58-0.92), and overall mortality (RR 0.45; 95% CI, 0.33-0.60). These results demonstrate that anticoagulant therapy improves SVT recanalization and reduces the risk of thrombosis progression without increasing major bleeding. The incidence of recurrent VTE remains substantial also in anticoagulated patients. Effects were consistent across different subgroups of patients.

Conflict of interest: COI declared - see note

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Key points

Anticoagulant therapy was associated with a high rate of splanchnic vein recanalization and low rate of thrombosis progression.

Major bleeding risk and overall mortality of patients with splanchnic vein thrombosis were reduced by anticoagulant therapy.

Abstract

Treatment of splanchnic vein thrombosis (SVT) is challenging and evidence to guide therapeutic decisions remains scarce. The objective of this systematic review and meta-analysis was to determine the efficacy and safety of anticoagulant therapy for SVT. MEDLINE, EMBASE, and Clinicaltrial.gov were searched from inception up to December 2019 without language restrictions to include observational studies and randomized controlled trials reporting radiological or clinical outcomes in patients with SVT. Pooled proportions and risk ratios (RR) with 95% confidence intervals (CI) were calculated using a random-effects model. Of 4312 records identified by the search, 97 studies including 7969 patients were analyzed. In patients receiving anticoagulation, the rates of SVT recanalization, SVT progression, recurrent VTE, major bleeding, and overall mortality were 58% (95% CI, 51-64), 5% (95% CI, 3-7), 11% (95% CI, 8-15), 9% (95% CI, 7-12), and 11% (95% CI, 9-14), respectively. The corresponding values in patients without anticoagulation were 22% (95% CI, 15-31), 15% (95% CI, 8-27), 14% (95% CI, 9-21), 16% (95% CI, 13-20), and 25% (95% CI, 20-31). Compared with no treatment, anticoagulant therapy obtained higher recanalization (RR 2.39; 95% CI, 1.66-3.44) and lower thrombosis progression (RR 0.24; 95% CI, 0.13-0.42), major bleeding (RR 0.73; 95% CI, 0.58-0.92), and overall mortality (RR 0.45; 95% CI, 0.33-0.60). These results demonstrate that anticoagulant therapy improves SVT recanalization and reduces the risk of thrombosis progression without increasing major bleeding. The incidence of recurrent VTE remains substantial also in anticoagulated patients. Effects were consistent across different subgroups of patients.

Key words: anticoagulants, Budd-Chiari syndrome, mesenteric veins, portal vein, splanchnic circulation.

Introduction

Splanchnic vein thrombosis (SVT) includes portal, mesenteric, or splenic vein thrombosis, and the Budd-Chiari syndrome (BCS).[1] While the incidence of deep vein thrombosis of the limbs and pulmonary embolism is about 70-270 per 100000 patients, the incidence of SVT is at least 25 times lower with the most and least common types being represented by portal vein thrombosis (PVT) and BCS, respectively.[2,3] Common risk factors for SVT include liver cirrhosis, solid cancer, and myeloproliferative neoplasms. SVT may also be related to transient risk factors (e.g. surgery, abdominal inflammation or infection, hormonal replacement therapy, or pregnancy) and is defined as unprovoked in 15-27% of cases.[3-5] In about one third of patients, SVT is incidentally detected during abdominal imaging performed for other reasons.[4-8]

Treatment of SVT is challenging and requires careful evaluation of risk factors for SVT progression, recurrence of VTE, and bleeding. The latter may be substantial in particular in patients with underlying cirrhosis and/or cancer, also due to frequent comorbidities such as thrombocytopenia and gastro-esophageal varices.[9] Several observational studies, which evaluated the effects of anticoagulant therapy on the rates of recanalization and progression, recurrent VTE, and bleeding in patients with SVT reported conflicting findings.[1,10] As a result of the large clinical variability of SVT and of the limited evidence available, current treatment recommendations vary widely across clinical practice guidelines, and the decisions about which patients need to be treated, the type, dose or duration of anticoagulant therapy are often made empirically.[1,9-13] A better understanding of the average risk of clinically relevant outcomes in patients with SVT may help physicians in daily clinical practice and inform the design of future studies.

The objective of this systematic review and meta-analysis was, therefore, to evaluate radiological and clinical outcomes in patients with SVT receiving or not anticoagulant therapy.

Methods

This study-level systematic review and meta-analysis was performed following the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines.[14]

The protocol was registered in the PROSPERO database (registration number CRD42019127870 - https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019127870).

Databases search and study selection

MEDLINE and EMBASE were searched from inception up to December 2019 for observational studies and randomized controlled trials (RCTs) involving patients with SVT. Furthermore, we searched clincaltrial.gov for ongoing or completed studies and screened references of relevant studies. No language restrictions were applied. The complete search strategy is given in Supplemental Table 1.

Two authors independently reviewed titles and abstracts identified from the databases search to select studies which met the following inclusion criteria: (i) diagnosis of SVT; (ii) observational study or RCT including ≥ 10 patients; (iii) availability of radiological (i.e. recanalization or progression of SVT) or clinical (i.e. recurrent VTE, major bleeding, and overall mortality) outcomes; (iv) anticoagulant treatment with low molecular-weight heparin (LMWH), unfractionated heparin, fondaparinux, vitamin K antagonists (VKAs), direct oral anticoagulants (DOACs), or no anticoagulant therapy. Exclusion criteria were any of the following: (i) study design different from those specified in inclusion criteria; (ii) inclusion of < 10 patients; (iii) anticoagulant therapy different from those specified in inclusion criteria.

Any disagreement was resolved through discussion or involving a third review author.

Data extraction and quality assessment

Two review authors independently extracted data from the included studies. A consensus between the two review authors or a discussion with a third review author resolved any disagreement.

The following data were extracted: methodological quality, study design, patient characteristics (e.g. age, sex), site, extension, and stage of SVT, risk factors for SVT, type and duration of anticoagulant treatment, radiological (i.e. recanalization or progression of SVT) or clinical (i.e. recurrent VTE, major bleeding, and overall mortality) outcomes. Published supplementary materials were searched for data of interest, and corresponding authors were contacted in case of missing information.

The risk of bias of the included studies and the summary of the risk of bias were evaluated using the ROBINS-I tool for observational studies and the Cochrane tool for RCTs.[15,16]

Study outcomes

The radiological outcomes included any grade of recanalization (partial or complete) and progression of SVT at follow-up imaging. The clinical outcomes were recurrent VTE (i.e. deep vein thrombosis of the lower or upper extremities, pulmonary embolism, recurrent SVT), major bleeding as defined by study authors or interpreted as major by the review authors, and overall mortality.

Statistical analysis

The logit transformed proportion and corresponding sampling variances were calculated. Pooled proportions and risk ratios (RR) with corresponding 95% confidence intervals (CI) were calculated using a random-effects model. Heterogeneity among the included studies was evaluated by visual inspection of forest plots and by DerSimonian-Laird estimator, and it was defined low, moderate, and high for I^2 values of 25%, 50%, and 75%, respectively.[17] In case of heterogeneity, we performed random-effect subgroup analysis to explore the effects of the following variables: (i) site of thrombosis (i.e. portal, mesenteric, splenic, Budd-Chiari syndrome, and multiple veins); (ii) stage of thrombosis (i.e. acute or recent -if ≤ 6 months-, chronic -if > 6 months-, mixed, not reported); (iii) clinical presentation (i.e. symptomatic, incidental, mixed, not reported); (iv) risk factor (i.e. transient, persistent risk factor or unprovoked SVT, multiple risk factors); (v) type of therapy (i.e. parenteral,

oral, mixed); (vi) duration of therapy (i.e. ≤ 6 months, > 6 months, not reported); (vii) study design (i.e. retrospective, prospective, ambispective, RCTs). We decided a-priori to include a study in one of the subgroups defined above according to patient or SVT characteristics if the latter were present in more than 75% of patients included in that study. A mixed effect model with restricted maximum-likelihood estimator was performed fitting the above specified variables as moderators, whenever available.

A sensitivity analysis was planned to evaluate the effects of anticoagulant therapy in patients with different underlying risk factors (e.g. liver cirrhosis, solid cancer, myeloproliferative neoplasms) and to evaluate the effect of different types of anticoagulant therapy (i.e. LMWH alone, LMWH followed by VKAs, VKAs alone, and DOACs) on radiological and clinical outcomes.

The presence of publication bias was assessed in patient receiving anticoagulation by funnel plot of logit transformed proportion versus standard error. Funnel plot symmetry was tested by performing the Egger's test. If the Egger's test confirmed asymmetry, we used the Duval and Tweedie's trim-and-fill procedure to compute an unbiased estimate of the effect size.

Statistical analyses were performed using R studio version 1.2.5001, "meta", "metafor", and "forestplot" packages.[18] Summary forest plots have been prepared with STATA/SE v.12 (StataCorp LP, College Station, TX, USA). P values < 0.05 were considered statistically significant.

Data Sharing Statement

For original data, please contact emanuele.valeriani@outlook.com.

Results

Figure 1 shows the PRISMA flow diagram. A total of 4309 records were identified from the literature search. Screening of clinicaltrial.gov database found three additional ongoing studies which had no results available. After removing 621 duplicates, 3544 records were excluded by title and abstract screening. Full-text evaluation allowed exclusion of 50 studies. Finally, a total of 97

studies including 7969 patients were considered in the analysis (the full list of included studies is available on Supplemental data).

The inter-reviewer agreement was excellent with a kappa statistic of 0.88.

Characteristics of included studies

Three studies were RCTs and 94 were observational with a prospective (n=20), retrospective (n=71), or ambispective (n=3) design. Study size ranged from 10 to 832 patients. At least one of the radiological outcomes was reported by 56 studies (57.7%), and at least one clinical outcome by 91 studies (93.8%). Median treatment duration was 8.4 months (range 0.4 to 108 months, 36 studies), and median follow-up was 28.6 months (range 6 to 144 months, 62 studies). The main characteristics of included studies are reported in Supplemental Table 2.

Risk of bias across domains was low, moderate, serious, and critical respectively in 0%, 13.8% (n=13), 70.2% (n=66), and 16.0% (n=15) of the observational studies. The risk of bias was high for blinding of participants and personnel in two RCTs, and for incomplete outcome data in one trial. The risk of bias summary is shown in Supplemental Figure 1 and Supplemental Table 3 for observational studies and in Supplemental Figure 2 for RCTs.

Characteristics of the overall study population

The main characteristics of the overall population are reported in Table 1. The mean age was 49.2 ± 10.3 years and 4404 (55.8%) patients were males. Patients with portal, mesenteric, or splenic SVT, Budd-Chiari syndrome, and multiple sites SVT were included respectively in 63 studies (3365/6192 patients, 54.3%), 35 studies (1015/4271 patients, 23.8%), 18 studies (452/3570 patients,12.7%), 25 studies (1153/3624 patients, 31.8%), and 64 studies (2297/5937 patients, 38.7%). A total of 57 studies specified whether SVT was acute/recent (2607/3424 patients, 76.1%) or chronic (770/3424 patients, 22.5%). The most common risk factors for SVT were liver cirrhosis (2578/5518 patients,

46.7%; 51 studies), followed by myeloproliferative neoplasms (1429/4598 patients, 31.1%; 43 studies), and solid cancer (1108/4787 patients, 23.1%; 42 studies). SVT was unprovoked in 25.1% of patients (770/3070 patients; 35 studies).

The most frequent types of anticoagulant treatment were LMWH followed by VKAs (1320/2672 patients, 49.4%; 40 studies), LMWH alone (1038/2365 patients, 43.9%; 24 studies), and VKAs alone (1892/5170 patients, 36.6%; 39 studies). DOACs were used in nine studies (142/1125 patients, 12.6%), either alone (96/142 patients, 67.6%; three studies) or in combination with other treatment (46/142, 32.4%; six studies). Anticoagulant treatment was withheld in 26.3% of patients (1424/5416; 66 studies). In addition to anticoagulant treatment, the use of systemic or catheter-directed thrombolysis was reported in 25 studies (207/2477 patients, 8.4%).

Radiological and clinical outcomes

Figure 2 and Supplemental Figures 3 to 12 show the radiological and clinical outcomes in patients receiving anticoagulation. In this group, 56 studies reported at least one radiological outcome and 91 studies at least one clinical outcome. The rate of partial or complete recanalization was 58% (95% CI, 51 to 64; I^2 = 82%; 1017/1771 patients; 55 studies), the rate of progression of SVT was 5% (95% CI, 3 to 7; I^2 = 40%; 52/1416 patients; 47 studies), and the rate of recurrent VTE 11% (95% CI, 8 to 15; I^2 = 81%; 266/3123 patients; 40 studies). Information on the type of recurrent VTE in patients receiving anticoagulation were available for 127 patients (47.7%; 17 studies) of whom 80 had recurrent SVT, 19 had stent or trans-jugular intrahepatic portosystemic shunt thrombosis, 19 deep vein thrombosis, 7 pulmonary embolism with or without deep vein thrombosis, and 2 had cerebral vein thrombosis. Major bleeding occurred in 9% (95% CI, 7 to 12; I^2 = 85%; 491/4413 patients; 62 studies) and overall mortality in 11% of patients (95% CI, 9 to 14; I^2 = 74%; 537/4501 patients; 76 studies).

Due to limited data availability, we could perform a sensitivity analysis only for the subgroup of patients with liver cirrhosis. Results were similar to the overall population in terms of SVT recanalization (68%; 95% CI, 62 to74), SVT progression (6%; 95% CI, 4 to 9), recurrent VTE (10%; 95% CI, 4 to 22), major bleeding (6%; 95% CI, 4 to 10), and overall mortality (9%; 95% CI, 6 to 14).

The rates of SVT recanalization seemed to vary across different types of anticoagulant treatment ($p = 0.02$) being slightly higher with DOACs and LMWH (Supplementary Figure 13). Conversely, the rates of thrombosis progression, recurrent VTE, major bleeding, and overall mortality appeared to be similar (Supplementary Figures 14 to 17).

In patients receiving anticoagulation, there was evidence for publication bias for progression of SVT, major bleeding, and overall mortality (Supplemental Figure 18).

The Duval and Tweedie's trim-and-fill procedure suggested significant variation in the effect size of anticoagulant treatment for progression of SVT, major bleeding, and overall mortality (Supplemental Figure 19).

The outcome data for patients not receiving anticoagulant treatment were available from 56 studies (Figure 3 and Supplemental Figures 20 to 24). The rate of partial or complete recanalization was 22% (95% CI, 15 to 31; $I^2 = 72\%$; 158/710 patients; 25 studies). Progression of SVT occurred in 15% (95% CI, 8 to 27; $I^2 = 71\%$; 55/383 patients; 20 studies), recurrent VTE in 14% (95% CI, 9 to 21; $I^2 = 41\%$; 55/498 patients; 18 studies), major bleeding in 16% (95% CI, 13 to 20; $I^2 = 25\%$, 154/991 patients; 30 studies), and overall mortality in 25% (95% CI, 20 to 31; $I^2 = 59\%$; 216/954 patients; 40 studies). Information on the type of recurrent VTE in patients who remained untreated was available for 14 patients (25.9%, 2 studies) of whom 11 had recurrent SVT, 2 had trans-jugular intrahepatic portosystemic shunt thrombosis, and one deep vein thrombosis.

Fifty-five observational studies and one RCT included both patients receiving anticoagulant treatment for SVT and untreated patients (Figure 4 and Supplemental Figures 25 to 29). The use of anticoagulant therapy was associated with higher recanalization (RR 2.39; 95% CI, 1.66 to 3.44; I^2

= 74%; 25 studies) and lower progression of thrombosis (RR 0.24; 95% CI, 0.13 to 0.42; I^2 = 0%; 20 studies), major bleeding (RR 0.73; 95% CI, 0.58 to 0.92; I^2 = 0%; 28 studies), and overall mortality (RR 0.45; 95% CI, 0.33 to 0.60; I^2 = 28%; 39 studies) compared with no treatment. The incidence of recurrent VTE was similar between the two groups (RR 0.91; 95% CI, 0.44 to 1.87; I^2 = 75%; 18 studies).

Additional analyses in patients receiving anticoagulant therapy

The heterogeneity for the effects of anticoagulant treatment on radiological and clinical outcomes varied from low to high between studies and within each category of the subgroups evaluated (Supplemental Figures 3 to 7 and Supplemental Table 4). The variables included in subgroup analysis (i.e. site or stage of SVT, clinical presentation, risk factor, type and duration of anticoagulant therapy, and study design) explained only a very small part of the inter-study heterogeneity (Supplemental Table 4). Residual inter-study heterogeneity was low for progression of SVT, moderate for overall mortality, and high for SVT recanalization, recurrent VTE and major bleeding, (Supplemental Table 4).

Due to missing information from the included studies, the type of risk factor (transient versus persistent risk factor-related or unprovoked SVT versus multiple), type of therapy (parenteral versus oral), and site of SVT (portal versus mesenteric veins versus Budd-Chiari syndrome versus multiple veins) were fitted as moderators in mixed-effect models. The amount of heterogeneity explained by the model was 26.3% for recanalization of SVT, 16.6% for major bleeding, 13.0% for recurrent VTE, 0.8% for progression of SVT, 0% for overall mortality. The test for residual heterogeneity was significant for all outcomes, indicating that other moderators not included in the model were influencing inter-study heterogeneity (data not shown and available upon request). However, a higher rate of recanalization was found for isolated mesenteric vein thrombosis (risk ratio 14.1;

95% CI, 1.1 to 189.7) and for SVT that was unprovoked or associated with persistent thrombotic risk factors (risk ratio 4.2; 95% CI, 1.3 to 14.0).

Discussion

The results of this systematic review and meta-analysis show that vein recanalization is achieved in more than half of patients receiving anticoagulation, with relatively low rates of thrombosis progression. The risk of recurrent VTE remains substantial despite treatment, and major bleeding may occur in about 10% of patients. The rate of vein recanalization was higher, and progression of thrombosis was lower in patients on anticoagulant therapy compared with those without. Furthermore, the estimation of the rates of relevant outcomes from a large population of patients with SVT may help in developing future studies and also in guiding the use of anticoagulant treatment for these patients.

The recanalization and progression of SVT have important prognostic implications given their relationship with hepatic function deterioration and bleeding risk. SVT may lead to hypertension in the splanchnic circulation and the development of portosystemic collaterals, which increase the risk of gastro-intestinal bleeding.[19-21] Data about the effects of anticoagulant treatment on radiological outcomes varied broadly across the studies, ranging from 5.2% to 100% for recanalization and from 0% to 30.0% for SVT progression.[22-27] We found that anticoagulant treatment may significantly improve radiological outcomes. However, there was high inter-study heterogeneity which was explained only in part by the variables considered. Patients with SVT associated with persistent thrombotic risk factors and unprovoked SVT, or isolated involvement of the mesenteric vein seemed to derive the largest benefits in terms of vein recanalization. These findings should be interpreted very cautiously since they may be influenced by unmeasured confounders such as duration of anticoagulation or use of additional treatments (e.g. thrombolysis).

However, the rates of recurrent VTE were not negligible in patients receiving anticoagulant treatment and were similar to the rates observed in untreated patients. This lack of benefit in the

main clinical efficacy outcome may question the need for anticoagulation, although the large variability in patient characteristics and, most of all, differences in anticoagulant regimens and treatment durations do not allow any firm conclusion.

Conversely, a statistically significant reduction in the other two clinical outcomes considered, major bleeding and overall mortality, was found in patients receiving anticoagulation. This is relevant since patients with SVT often have multiple bleeding risk factors which may induce physicians to avoid anticoagulation and because previous studies failed to provide convincing evidence on the effect on mortality. If on the one hand this finding supports the treatment of patients with SVT, in particular by suggesting a possible safety benefit associated with recanalization and prevention of new onset or worsening of portal hypertension, on the other hand we need to acknowledge that selection bias due to the choice of not treating sicker patients and those with a poor prognosis may have had an impact on our results.

The current work has several limitations which warrant discussion. First, the studies included were heterogenous in terms of patient characteristics, underlying risk factors, vein involvement, anticoagulant treatment, and duration of follow-up. This variability may have resulted in the high heterogeneity of effects of anticoagulant therapy and may affect the external validity of the results. The size of the study population and the availability of some clinical and study-related variables allowed us to explore inter-study heterogeneity which was, however, only partly explained by the analysis leaving the risk for residual confounding. Second, the evaluation of all outcomes on a study-level basis represents an intrinsic design limitation of study-level meta-analysis. This hampered an in-depth analysis on the impact of specific characteristics (e.g. site of thrombosis or different anticoagulant treatments) on the outcomes. Similarly, the efficacy and safety of anticoagulant therapy could not be assessed in relation to patient specific risk factors like solid cancer, or myeloproliferative neoplasms. Subgroup analysis and sensitivity analysis suggested that the effects of anticoagulant treatment on radiological and clinical outcomes were consistent across different subgroups of patients including those with liver cirrhosis. Third, all included studies were

at risk of bias (Supplemental Table 3 and Supplemental Figure 1 and 2) which potentially limits the external validity of the results and underlines the urgent need of high-level evidence in this field. Fourth, only one study randomized patients to anticoagulant therapy versus no treatment.[28] All measures of effect were largely derived from cohort studies in which the decision to use a specific agent or withhold anticoagulation was not randomized and could be influenced by patient characteristics and prognosis. Therefore, all comparisons among different types of anticoagulant agents or between anticoagulation and no treatment remain exploratory and need to be taken cautiously. A proportion of patients received concomitant antiplatelet therapy, mostly in cases with underlying myeloproliferative neoplasms. Poor reporting precluded additional analysis on this subgroup of patients. Finally, there was evidence of significant publication bias for the effects of anticoagulant treatment on progression of SVT, major bleeding, and overall mortality. This is consistent with the possibility that small studies with large effect size were not published. However, it is unlikely that the latter were missed by our systematic search that considered several databases without study size restriction.

In conclusion, anticoagulant therapy for SVT is associated with vein recanalization and low probability of thrombosis progression. The risks of recurrent VTE and major bleeding in patients on anticoagulation and the proportion of events in those left untreated strongly suggest the need for additional studies to optimize SVT management.

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Authorship contributions

Study conception and design: E.V., M.D.N., N.R., W.A.; Data acquisition: E.V., O.C., M.D.N., N.R.; Statistical analysis: E.V., M.D.N., N.R.; Interpretation of the data: All authors; Drafting of the manuscript: All authors; Critical revision of the manuscript for important intellectual content: All authors; Final approval of the manuscript: All authors.

Conflict of Interest Disclosure

E.V., N.R., O.C., J-C.G-P., M.M., and E.P. has nothing to disclose. M.D.N. reports personal fees from Bayer, Daiichi Sankyo, Pfizer, Leo Pharma, and Aspen, outside the sub- mitted work; W.A. has received a research grant from Bayer to support a clinical study in patients with splanchnic vein thrombosis, received honoraria for participation at advisory boards from Bayer, Boehringer Inghelheim, Daiichi Sankyo, BMS/Pfizer, Sanofi, and Portola, and reports grants and personal fees from Bayer, and personal fees from BMS/Pfizer, Daiichi Sankyo, Sanofi, Aspen, Janssen, and Portola, outside the submitted work.

Data Sharing

For original data, please email the corresponding author.

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Table 1: Characteristics of study population (n=7969) from 97 studies

		Studies reporting the variable, n
Patients characteristics		
Age, mean (SD), years	49.2 ± 10.3	91
Male sex, no./No. (%)	4404/7886 (55.8)	95
Site of SVT		
Portal vein thrombosis, no./No. (%)	3365/6192 (54.3)	63
Mesenteric vein thrombosis, no./No. (%)	1015/4271 (23.8)	35
Splenic vein thrombosis, no./No. (%)	452/3570 (12.7)	18
Budd-Chiari syndrome, no./No. (%)	1153/3624 (31.8)	25
Multiple sites thrombosis, no./No. (%)	2297/5937 (38.7)	64
Not reported, no./No. (%)	55/220 (25.0)	6
Vein involvement		
Partial, no./No. (%)	521/853 (61.1)	20
Complete, no./No. (%)	306/853 (35.9)	20
Not reported, no./No. (%)	26/853 (3.0)	20
Stage of thrombosis		
Acute/recent, no./No. (%)	2607/3424 (76.1)	57
Chronic, no./No. (%)	770/3424 (22.5)	57
Not reported, no./No. (%)	47/3424 (1.4)	57
Risk factors		
Liver cirrhosis, no./No. (%)	2578/5518 (46.7)	51
Myeloproliferative neoplasm, no./No. (%)	1429/4598 (31.1)	43
Unprovoked, no./No. (%)	770/3070 (25.1)	35
Solid cancer, no./No. (%)	1108/4787 (23.1)	42
Surgery, no./No. (%)	642/3762 (17.1)	44
Abdominal inflammation/infection, no./No. (%)	726/4346 (16.7)	41
Hormonal replacement therapy, no./No. (%)	297/3250 (9.1)	31
Thrombophilia		
JAK2 V617F, no. positive/No. tested (%)	148/802 (18.5)	9
Antiphospholipid syndrome, no. positive/No. tested (%)	135/1064 (12.7)	20
Factor V Leiden mutation, , no. positive/No. tested (%)	224/1938 (11.6)	28
Protein C and/or S deficiency, no. positive/No. tested (%)	125/1085 (11.5)	21
Prothrombin G2021A mutation, no. positive/No. tested (%)	112/1257 (8.9)	15
Antithrombin III deficiency, no. positive/No. tested (%)	30/904 (3.3)	13
Diagnosis of SVT		
Computed tomography, no./No. (%)	3418/4973 (68.7)	56
Doppler ultrasonography, no./No. (%)	1794/4645 (38.6)	49
Angiography, no./No. (%)	265/2627 (10.1)	16
Magnetic resonance imaging, no./No. (%)	297/3633 (8.2)	24
Peri-operative, no./No. (%)	153/2378 (6.4)	13
Follow-up imaging		
Ultrasonography, no./No. (%)	484/494 (98.0)	13
Computed tomography, no./No. (%)	507/678 (74.8)	16
Median follow-up, months	28.6 (6 to 144)	62
Parenteral anticoagulation		
LMWH, no./No. (%)	1038/2365 (43.9)	24
LMWH or UFH, no./No. (%)	383/1785 (21.5)	13
Fondaparinux, no./No. (%)	26/703 (3.7)	2
Oral anticoagulation		
LMWH→VKAs, no./No. (%)	1320/2672 (49.4)	40
VKAs, no./No. (%)	1892/5170 (36.6)	39
DOACs, no./No. (%)	142/1125 (12.6)	9
Antiplatelet therapy	189/2569 (7.4)	15
Mixed strategies, no./No. (%)	505/1817 (27.8)	22
No anticoagulation, no./No. (%)	1424/5416 (26.3)	66
Systemic or Catheter directed thrombolysis, no./No. (%)	207/2477 (8.4)	25
Median treatment duration, months	8.4 (0.4 to 108)	36
Other therapeutic procedures		
Thrombectomy/stenting, no./No. (%)	176/1656 (10.6)	16
TIPS, no./No. (%)	482/2960 (16.3)	26
Liver transplantation, no./No. (%)	191/1634 (11.7)	20
Surgery, no./No. (%)	154/1259 (12.2)	20

DOACs, direct oral anticoagulants; LMWH, low-molecular-weight heparin; SVT, splanchnic vein thrombosis; TIPS, trans-jugular intrahepatic portosystemic shunt; UFH, unfractionated heparin; VKAs, vitamin K antagonists

Titles and Legends of Figures

Title Figure 1: PRISMA flow diagram

Legend Figure 1: The diagram indicates the flow of the systematic review

Title Figure 2: Radiological and clinical outcomes in patients receiving anticoagulant therapy

Legend Figure 2: CI, confidence intervals; SVT, splanchnic vein thrombosis; VTE venous thromboembolism

Title Figure 3: Radiological and clinical outcomes in patients without anticoagulant therapy

Legend Figure 3: CI, confidence intervals; SVT, splanchnic vein thrombosis; VTE venous thromboembolism

Title Figure 4: Radiological and clinical outcomes in treated vs untreated patients

Legend Figure 4: CI, confidence intervals; RR, risk ratio; SVT, splanchnic vein thrombosis; VTE venous thromboembolism

Figure 1

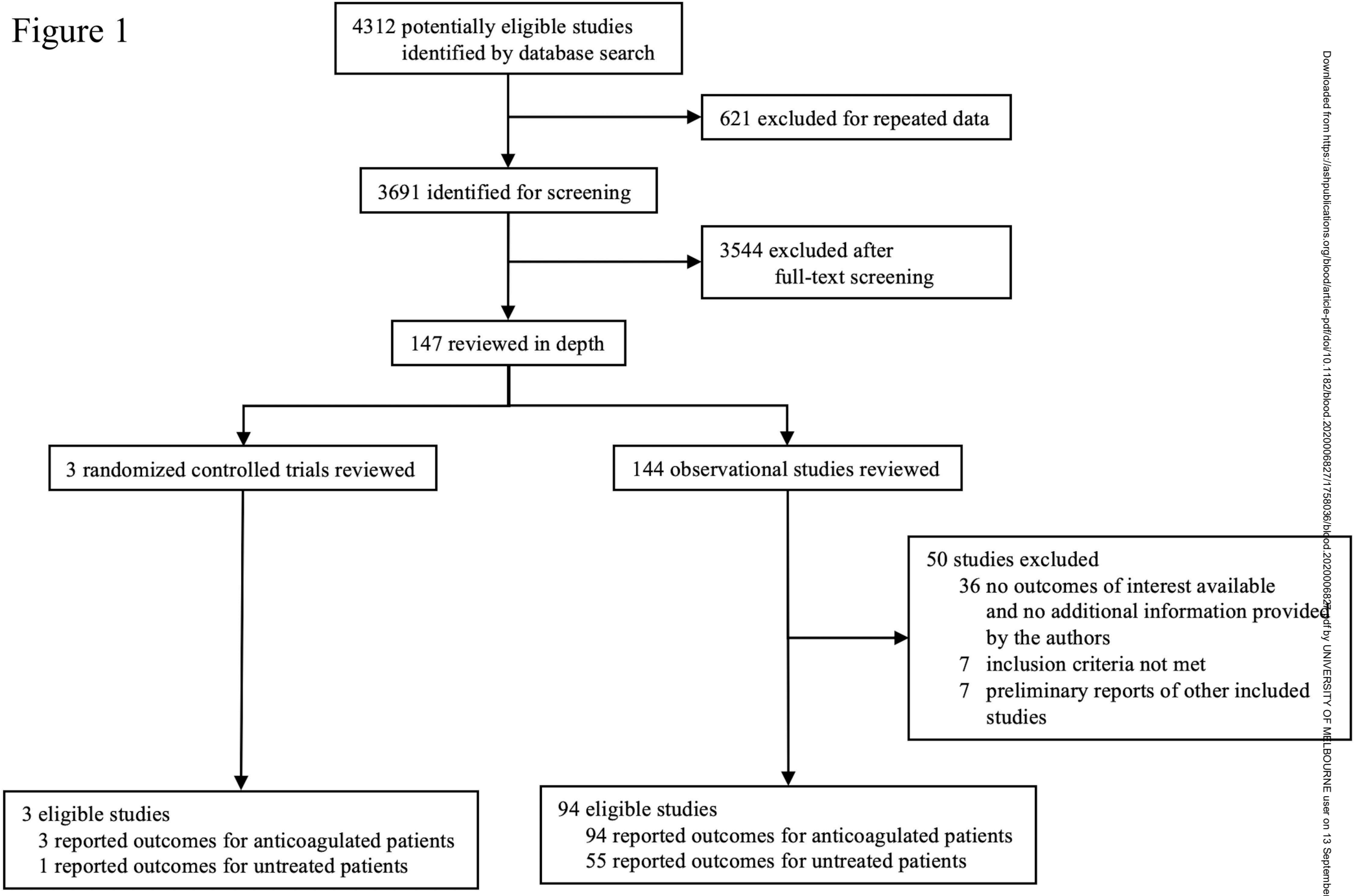
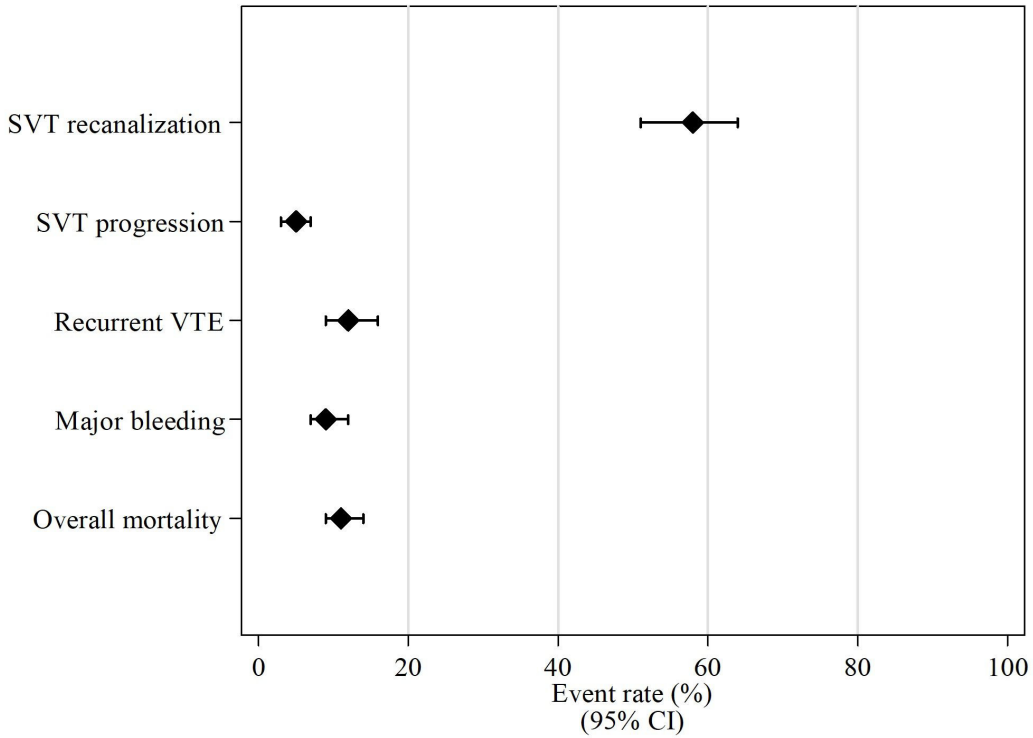
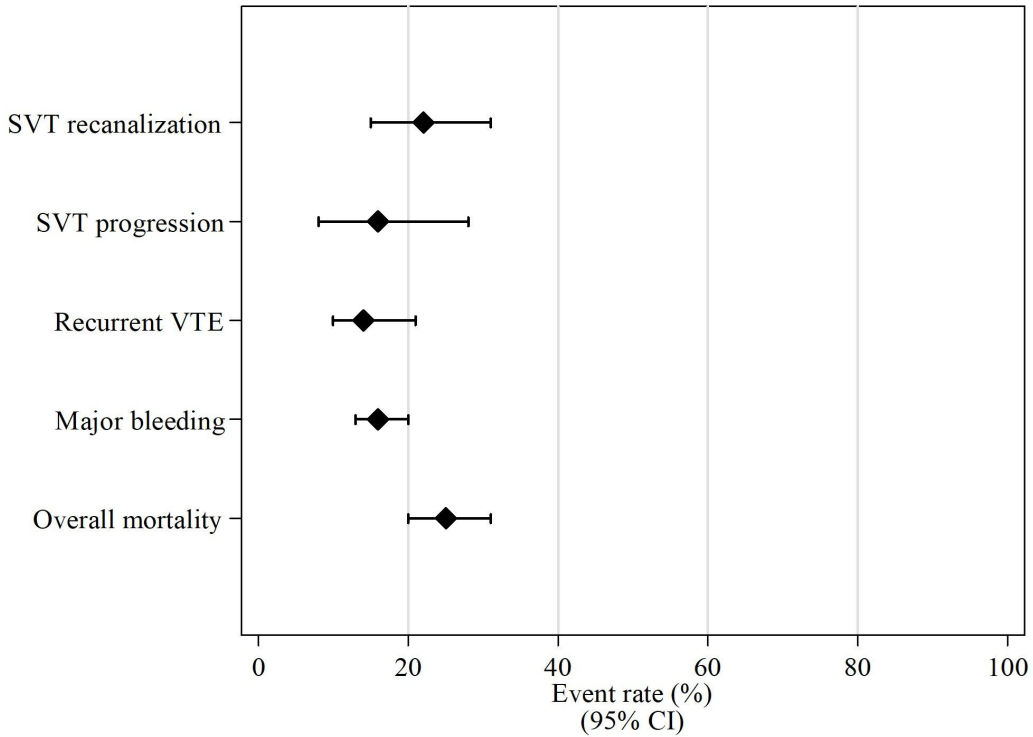


Figure 2



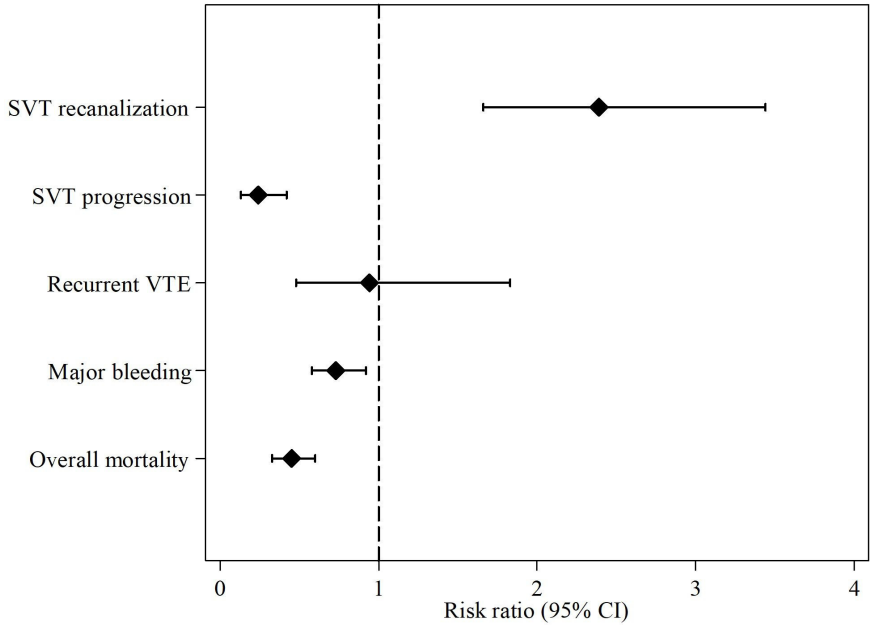
Outcome	Events (no./No.)	Studies (no.)	I^2 (%)	Event rate (%) (95% CI)
SVT recanalization	1017/1771	55	82	58 (51-64)
SVT progression	52/1416	47	40	5 (3-7)
Recurrent VTE	266/3123	40	81	11 (8-15)
Major bleeding	491/4413	62	85	9 (7-12)
Overall mortality	537/4501	76	74	11 (9-14)

Figure 3



Outcome	Events (no./No.)	Studies (no.)	I^2 (%)	Event rate (%) (95% CI)
SVT recanalization	158/710	25	72	22 (15-31)
SVT progression	55/383	20	71	15 (8-27)
Recurrent VTE	55/498	18	41	14 (9-21)
Major bleeding	154/991	30	25	16 (13-20)
Overall mortality	216/954	40	59	25 (20-31)

Figure 4



Outcome	Anticoagulated: events (no./No., %)	Untreated: events (no./No., %)	Studies (n)	I^2 (%)	RR (95% CI)
SVT recanalization	381/667 (57.1)	158/710 (22.3)	25	74	2.39 (1.66-3.44)
SVT progression	16/454 (3.5)	55/383 (14.4)	20	0	0.24 (0.13-0.42)
Recurrent VTE	140/1350 (10.3)	55/498 (11.0)	18	75	0.91 (0.44-1.87)
Major bleeding	287/1927 (14.9)	154/967 (15.9)	28	0	0.73 (0.58-0.92)
Overall mortality	221/1789 (12.2)	204/913 (22.6)	39	28	0.45 (0.33-0.60)