Treatment of Splanchnic Vein Thrombosis with Anticoagulant Therapy in Patients with Cancer and Myeloproliferative Neoplasm

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Abstract

Venous thromboembolism (VTE) is a frequent complication in patients with cancer and myeloproliferative neoplasms (MPN). Approximately 4 to 20% of patients with cancer experience VTE at some disease stage and the overall thrombosis risk is as high as 20% in patients with MPN. VTE includes deep vein thrombosis (DVT) (e.g., lower extremities, splanchnic veins, etc.) and pulmonary embolisms (PE). Splanchnic vein thromboses (SVTs) are rare VTEs that include splenic, mesenteric, portal, and hepatic vein thromboses that occur in the veins that drain a major portion of the digestive system. Without treatment, SVTs can expand and may lead to complications such as mesenteric ischemia, Budd-Chiari syndrome, major bleeding, and mortality. There is high variability in the incidence, site, and type of SVTs reported in the medical literature.

SVTs are frequently occurring in patients with cancer or MPN given their hypercoagulable state. Recommendations from clinical practice guidelines on the management of SVTs are derived from small observational studies or expert consensuses. While anticoagulant therapy is often recommended to treat SVTs in patients with cancer or MPN, type and dosing of anticoagulant along with their respective effectiveness and safety profiles remain unclear. To address these important knowledge gaps, we performed a systematic review of the literature using EMBASE, MEDLINE, and CENTRAL databases to identify studies comparing effects of anticoagulant therapy for the management of SVTs in patients with cancer or MPN. Anticoagulant therapy seems to increase the risk of clinically-relevant bleeding by 2-fold (incidence rate ratio (IRR): 2.22 (95% confidence intervals (CI): 1.02-4.86)) without decreasing the rate for recurrent VTE (IRR: 0.86 (95% CI: 0.29-2.55)) or all-cause mortality (IRR: 0.71 (95% CI: 0.34-1.48)) among patients with cancer. In patients with MPN and SVT, anticoagulant

therapy decreased the risk of recurrent VTE (IRR: 0.49 (95% CI: 0.32- 0.74)) without increasing the risk of clinically-relevant bleeding (IRR: 0.53 (95% CI: 0.26-1.07)) or all-cause mortality (0.17 (95%CI: 0-8.40)).

A survey of practice was then conducted to assess practice variation among Canadian VTE specialists. The online survey was distributed by three national hematology organizations (Thrombosis Canada, CanVECTOR, and Canadian Hematology Society). All respondents agreed that a parenteral low molecular weight heparins (LMWH) or direct oral anticoagulants (DOAC) were effective for the management of SVT in patients with cancer, while 89% reported that these anticoagulant regimens were not associated with heightened risk of clinically-relevant bleeding complications in patients with MPN. A total of 80% were interested in participating in a randomized controlled trial (RCT) comparing DOAC and LMWH in patients with SVT and cancer or MPN, while 56% were interested in participating in a placebo-controlled RCT of anticoagulation in patients with SVT and cancer or MPN. The responses on the minimal clinically important difference (MCID) to lower the rate of recurrent VTE required for a RCT comparing two different types of anticoagulants (e.g., DOAC vs. LMWH) were heterogenous but 50% of respondents reported that an increase of 1% in clinically-important bleeding would be reasonable to use a DOAC instead of LMWH and lead to change in clinical practice.

Results of these investigations were then used to develop a protocol for a pilot RCT comparing DOACs to LMWH for the management of SVT in patients with cancer. The pilot trial will assess the feasibility of a non-inferiority RCT comparing therapeutic dose of DOAC to LMWH for 6 months in patients with acute, symptomatic objectively-diagnosed SVT and active cancer. The feasibility outcomes include rates of recruitment, retention, and adherence to study procedures.

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1. Thesis Outline

This thesis includes three manuscript that are in preparation for submission to peer-reviewed journals:

- Treatment of Splanchnic Vein Thrombosis with Anticoagulant Therapy in Patients with Cancer: A Systematic Review and Meta-Analysis.
- Delphi Survey of Canadian Physicians to Determine Optimal Anticoagulant Treatment Approaches for Patients with Cancer and Splanchnic Venous Thrombosis.
- Treatment of Splanchnic Venous Thrombosis in Patients with Cancer (SVT-CA) using LMWHs and DOACs: Protocol for a Pilot Randomized Controlled Trial.

2. Treatment of Splanchnic Vein Thrombosis with Anticoagulant Therapy in Patients with Cancer: A Systematic Review and Meta-Analysis

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Abstract

Background: Cancer and myeloproliferative neoplasm (MPN) are major risk factors for splanchnic vein thromboses (SVTs). Data on the management of SVT is scarce. Hence, clinical practice recommendations are mostly derived from expert opinions.

Aims: We sought to determine the clinical effectiveness and safety of anticoagulant therapy in adult patients with either cancer- or MPN-associated SVTs.

Methods: EMBASE, MEDLINE, CENTRAL, and Clinicaltrials.gov were searched for randomized controlled trials (RCTs) and observational studies from inception to April 30, 2021. The primary outcome was rate of recurrent venous thromboembolism (VTE). Secondary outcomes included rate of vein recanalization, SVT extension/progression, clinically-relevant bleeding, and all-cause mortality. Incidence rates and incidence rate ratios (IRR) along with their respective 95% confidence intervals (CIs) were generate for the different outcomes.

Results: 3331 studies were identified and 17 studies (12 full-text publications and 5 abstracts) were included, most being retrospective cohorts. There were no RCTs. 1310 patients (27.6% cancer and 72.4% MPN) were included, 78.8% received anticoagulation. Mean age was 53.2 +/- 8.3 years and 48.3% patients were male. Patients with cancer mostly received low molecular weight heparins (LMWH) (mean duration: 6.6 +/- 2.6 months), while patients with MPN most received vitamin K antagonists (VKA) (mean duration: 17.78 +/- 8.5 months). Anticoagulation increased the risk of bleeding by two-fold in patients with cancer (IRR: 2.22, 95% CI: 1.02-4.86). It also reduced the risk of recurrent VTE by half in patients with MPNs (IRR: 0.49, 95% CI: 0.32-0.74), with no increase in the risk of clinically-relevant bleeding or all-cause mortality.

Conclusion: Anticoagulation therapy increased the risk of clinically-relevant bleeding without decreasing the risk of recurrent VTE or all-cause mortality in patients with cancer. Anticoagulant therapy reduced the risk of recurrent VTE without increasing the risk of clinically-relevant bleeding in patients with MPN. Well-designed RCTs are needed in these patient populations.

Introduction

Splanchnic vein thrombosis (SVT) is a form of unusual site venous thromboembolism (VTE). It includes splenic, mesenteric, portal, and hepatic vein thromboses which occurs with obstruction to the hepatic venous outflow.[1] SVTs arise in the splanchnic venous circulation that drains the digestive system from the lower esophagus to the upper areas of the rectum and can lead to mesenteric ischemia, Budd Chiari syndrome, or death.[2] Compared to usual site VTE (e.g., pulmonary embolism (PE) and lower limb deep vein thrombosis (DVT)), which occurs in 1.5 per 1,000 individuals annually, SVTs seem to have a 25 times lower incidence.[2] However, there is considerable variability in the incidence of SVT reported in the literature based on diagnostic tests used as well as the site and type of SVTs.[3] Recently, a large retrospective cohort study reported that SVT incidence is rising, highlighting the need to investigate treatment strategies.[4] This increased incidence may result from increased use of Computed Tomography (CT) scans and their better detection accuracy. Hence, more incidental SVTs may be important contributors to the increased incidence, especially in patients with cancer given that they are undergoing frequent staging imaging for their underlying malignancy.

Cancer is an important risk factor which is present in approximately 30% of patients with SVT.[5,6] Myeloproliferative neoplasms (MPNs) are also among the leading systemic causes of SVT, with a prevalence of about 10% in SVT patients.[7,8] SVTs are associated with important morbidity and mortality compared to the general population in these patient populations.[4,5,9] Patients with SVTs have a significantly reduced survival compared to matched controls, particularly those with cancer and cirrhosis, and patients who received anticoagulant treatment (23.9%) may have better clinical outcomes.[4] A large prospective cohort of patients with objectively-confirmed SVT showed that cancer and MPN were associated with 6.23 and 9.02 times

higher hazard risk of thrombotic events (including recurrent SVT, symptomatic VTE, arterial thrombosis, and mesenteric infarction), respectively.[5]

The American Society of Hematology suggests treatment with an initial 3-6 months of anticoagulation or observation for patients with cancer and splanchnic/visceral vein thrombosis (Conditional recommendation; very low certainty of evidence)[10]. Guidelines providing recommendation for the management of SVT are currently based on limited evidence, mostly coming from expert opinions and small observational studies.[11] Hence, the anticoagulant type, duration, and dosing for patients with SVT and cancer or MPN remains largely unknown. We sought to assess the efficacy and safety of anticoagulant therapy in these patient populations.

Methods

This systematic review and meta-analysis was produced using guidelines from the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) Statement.[12] The study protocol was registered on the Open Science Framework, a free and open-source project management tool. The protocol can be found here: https://doi.org/10.17605/OSF.IO/4SAVK.

Databases and Reference Searching

The search strategy was developed in consultation with a medical librarian at the University of Ottawa. EMBASE, MEDLINE, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to April 30, 2021, without any restrictions on language, publication year, or study size. References of included studies and ClinicalTrials.gov

were also searched for relevant studies. Searched studies were uploaded on the systematic review software Covidence and deduplicated to prepare for screening.

Study Eligibility

Peer-reviewed observational studies and randomized controlled trials (RCTs) were included if they consisted of, or included a subpopulation of, adult patients with SVT and either cancer or MPN who were given anticoagulants for treatment of their SVTs. To be included, studies also needed to report data on the type of anticoagulant therapy used and at least one of the study's outcomes of interest. The primary outcome was rate of recurrent VTE. Secondary outcomes included rate of vein recanalization, SVT progression/extension, clinically-relevant bleeding, and all-cause mortality. Vein recanalization was assessed for either complete or partial status, or no changes after anticoagulation during follow-up; recurrent VTE as imaging-confirmed recurrent SVT, upper/lower extremity DVT, PE, or unusual site thromboses during follow-up; SVT progression/extension as thrombosis progression during follow-up; and clinically-relevant bleeding included major bleeding[13] and clinically relevant non-major bleeding[14] as defined by the International Society on Thrombosis and Haemostasis (ISTH)).

Studies were excluded if they included only pediatric patients. Case reports, editorials, commentaries, notes, letters, opinions, and book chapters were also excluded. Due to the scarcity of clinical evidence in the patient population under study, studies with abstracts only, and no full-text peer-reviewed publications, were included if they otherwise met our study's criteria.

The title and abstract of searched studies were independently screened by two investigators, followed by screening of the study's full texts. Reasons for excluding any study were

summarised in a PRISMA flow diagram (**Figure 1**). Any conflicts were resolved by consensus or discussion with the third reviewer.

Data Extraction

Data of the included studies were extracted using a standardized form, after two investigators independently piloted the first 5 studies. The study's design, centers, and duration, as well as the participant's age, sex, characteristics of cancer or MPN (site, location, stage, size, and number), Eastern Cooperative Oncology Group (ECOG) status, Child-Pugh score, history of VTE, receipt of chemotherapy treatment, characteristics of SVT (number, location, and type), dose/frequency/duration/type of anticoagulation, and the described efficacy/safety outcomes were extracted, if available. The corresponding author of studies were contacted for more information or for clarification as needed.

Risk of Bias Assessments

The Cochrane Risk of Bias 2 Tool and Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) tool were used to evaluate risk of bias for RCTs and observational studies, respectively. The Cochrane Risk of Bias 2 Tool contains 5 domains and an overall risk of bias, which include bias from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result, overall risk of bias, and a final judgement on whether the study is of low risk, high risk, or has some concerns.[15] ROBINS-I assesses the following in non-randomized studies: confounding, selection bias, bias in measurement classification of

interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported result.[16]

Data Synthesis and Meta-Analyses

Continuous variables were reported in either mean and standard deviation, or median and interquartile range, and categorical variables were reported as counts, with percentages. Individual study estimates were converted to rates per patient-years of follow-up. The person-years of follow up provided by the study (if reported) was used. If the person-years of follow-up were not available, estimates were computed by multiplying the mean or median follow-up duration by the number of participants. Pooled incidence rate ratios (IRR) and 95% confidence intervals (CI) were generated through meta-analysis by calculating random effects estimates using the Mantel-Haenszel method. Pooled rates and 95% CI were then converted back to rates per patient-years of follow-up.

Forest plots of relative risks were generated, with I^2 statistics to assess study heterogeneity. An I^2 statistic of 0-30% was considered non-significant heterogeneity; 30-75% represented moderate heterogeneity; and 75-100% represented considerable heterogeneity. Otherwise, a random effects model was used to pool the results because, compared to the fixed-effect model, it assumes that estimates of treatment effects may vary across studies. Publication bias was examined weighted linear regression of study treatment effect on its standard error, using inverse variance weighting and Egger's test.[17] Statistical analyses were conducted using R studio version 4.2.1. $p < 0.05$ was considered to be statistically significant.

Results

After screening for eligibility, 17 studies were included in the analysis (**Figure 1**). 13 (76.5%) studies were retrospective cohorts, 3 (17.6%) were case series, and 1 (5.9%) was a prospective registry (**Table 1**). No RCTs were identified from the literature. A total of 7 (41.2%) studies only included patients with cancer (361, 27.6%) whereas 10 (58.8%) studies only included patients with MPN (949, 72.4%). Out of 1310 included patients, 1032 (78.8%) received anticoagulant therapy, while 278 (21.2%) patients did not receive any anticoagulation (e.g., observation, antiplatelet agents, or other therapies) (**Table 1**). The mean age of patients was 53.2 +/- 8.3 years and 633 (48.3%) patients were male. Most patients with cancer and SVT received low molecular weight heparins (LMWHs) (111, 61.7%), followed by vitamin K antagonists (VKAs) (60, 33.3%). Patients with MPN and SVT most frequently received VKAs (426, 71.1%), followed by LMWH (172, 20.2%). The mean (+/- standard deviation) duration of anticoagulation for patients with cancer and MPN were 6.6 +/- 2.6 months and 17.78 +/- 8.5 months, respectively.

In patients with cancer, the most common cancer types were pancreatic (138, 38.2%), followed by hepatobiliary (66, 18.3%), and gastrointestinal (GI) tract (53, 14.7%). In terms of SVTs, the most common involved sites were portal vein (123, 34.1%) and superior/inferior mesenteric vein (51, 14.1%). In patients with MPNs, the most common diagnoses were polycythemia vera (PV) (356, 37.5%) and essential thrombocythemia (ET) (288, 30.3%). Most common SVTs were in portal (555, 58.5%) and hepatic veins (213, 22.4%) (**Table 1**).

Risk of Bias

Most studies had a high degree of bias due to confounding, inherent in the non-randomized design of the observational studies or due to lack of controlling for covariates (**Figure 8**). Many

studies did not provide details on anticoagulation regimens, and some did not define their intervention/control groups or follow-ups in adequate details, leading to bias in classification of interventions or measurement of outcomes.

Primary and Secondary Outcomes in Patients with Cancer

A total of four studies reported recurrent VTE; anticoagulated patients had an incidence rate of 5.1 (95% CI: 2.5-10.4; I^2 = 0.0%) per 100 patient-years (**Table 2**), whereas untreated patients had a rate of 7.5 (95% CI: 3.3-17.0; I^2 = 14%) per 100 patient-years (**Table 3**), with an overall IRR of 0.86 (95% CI: 0.29-2.55; I^2 = 0.0%) (**Table 4**).

Only three studies (Kim et al.[18], Bozas et al.[19], and Acuna-Villaorduna et al[20]) reported the occurrence of vein recanalization. Complete resolution of SVT, described as patency of the portal vein system on follow-up imaging in patients who received anticoagulation or did not, had an incidence rate of 15.6 (95% CI: 7.0-34.8; I^2 = 0.0%) and 17.6 (95% CI: 8.4- 36.8; I^2 = 0.0%) per 100 patient-years, respectively (**Table 2 and 3)**, with an IRR of 1.15 (95% CI: 0.36-3.65; I^2 = 0.0%). Two studies reported SVT progression/extension: incidence in anticoagulated and non-treated patients was 29.8 (95% CI: 13.8- 64.4; I^2 = 0.0%) and 30.5 (95% CI: 19.9-46.7; I^2 = 0) per 100 patient-years, respectively (**Table 2 and 3**), with an of IRR of 0.95 (95% CI: 0.39-2.28; I^2 = 0.0%) (**Table 4**). Patients with cancer who received anticoagulation had a higher risk of clinically-relevant bleeding compared to patients who did not receive anticoagulant therapy (IRR: 2.22 (95% CI: 1.02-4.86; I^2 = 0%)) (**Table 4**), with incidence rates of 7.8 (95% CI: 2.6-23.7; I^2 = 77.0%) compared to 4.8 (95% CI: 1.5-15.7; I^2 = 37%) per 100 patient-years, respectively. Three studies reported on the incidence of all-cause mortality, demonstrating an overall 29% lower risk with anticoagulation, although not statistically significant (IRR: 0.71; 95% CI: 0.34-1.48; I^2 = 0%)

(**Table 4**). The anticoagulated cohort had an incidence of 45.5 (95% CI: 27.1-76.5; I^2 = 32.0%) while untreated patients had an incidence of 61.1 (95% CI: 15.9-234.9; I^2 = 82%) per 100 patient-years.

Primary and Secondary Outcomes in Patients with MPN

Anticoagulant therapy led to reduction of risk of recurrent VTE by 51% (IRR: 0.49 (95% CI: 0.32-0.74; I^2 = 0%) (**Table 7**), with incidences of 2.2 (95% CI: 1.1-4.2; I^2 = 80%) and 4.4 (95% CI: 2.2-9.0; I^2 = 75%) per 100 patient-years in anticoagulated and non-anticoagulated patients, respectively (**Table 5 and 6**). None of the included studies reported incidences of vein recanalization or SVT progression/extension in patients with MPN (**Table 5-7**). Three studies reported clinically-relevant bleeding, with an overall IRR of 0.53 (95% CI: 0.26-1.07; I^2 = 0%) (**Table 7**); anticoagulated patients had an incidence rate of 3.1 (1.8-5.4; I^2 = 47%) and untreated patients had a rate of 6.0 (95% CI: 2.4-14.9; I^2 = 45%) per 100 patient-years (**Table 5 and 6**). Finally, only one study reported all-cause mortality and no patients died (**Table 7**).

There was no evidence for publication bias for recurrent VTE, clinically-relevant bleeding, or all-cause mortality, in either patient populations (**Figure 9**).

Discussion

Anticoagulant therapy seems to be associated with a higher risk of clinically-relevant bleeding for patients with SVT and cancer compared to those not treated with anticoagulation. However, the risks of recanalization, recurrent VTE, SVT progression/extension, and all-cause mortality were only moderately reduced or similar between patients with SVT and cancer receiving anticoagulant therapy or not. Patients with MPN and SVTs who received anticoagulation had

lower the risk of recurrent VTE compared to untreated patients. Anticoagulated patients also seem to have a lower risk of clinical-relevant bleeding.

Patients with cancer receiving anticoagulation for SVTs did not seem to demonstrate improvement in clinical outcomes compared to those not receiving this anticoagulant therapy while patients with MPN seem to benefit from anticoagulant therapy. There are limited data available regarding the efficacy, safety, or duration of anticoagulant therapy for SVTs in patients with cancer as SVTs were not included in randomized trials assessing different anticoagulant regimens for the management of cancer-associated thrombosis[21]. One available clinical practice guideline on the management of SVT was published by the National Comprehensive Cancer Network (NCCN). The NCCN guideline made a weak recommendation for patients with cancer and acute SVTs to receive anticoagulant therapy if there are no contraindications to treatment[22]. Parameters such as diagnostic certainty, symptomology, thrombosis degree, and duration of thrombosis need to be considered by clinicians to decide on initiation of anticoagulation[10,23].

LMWHs and VKAs seem to be the standard of care anticoagulants for treating SVTs [24–26]. However, best management options in patients with cancer remain unclear. LMWH, VKAs, and direct oral anticoagulants (DOACs) have been used in this patient population.[18] A retrospective cohort study of 50 patients with liver cirrhosis and portal vein thromboses (PVTs), but no cancer, found that 14 (70%) of patients given edoxaban had complete resolution of PVT compared to only 6 (20%) of patients who received VKAs.[27] Clinically-relevant GI bleeding was seen in 3 (15%) of patients who received edoxaban and in 2 (7%) of those who received VKAs. Our findings seem to be consistent with current recommendations for the management of patients with SVT. For patients with SVT and cancer, the use of LMWH and VKA appeared to not reduce rate of recurrent VTE or all-cause mortality but increased the risk of clinically-relevant bleeding, particularly in the GI

tract. A narrative review[28] suggested that anticoagulation may be recommended in patients with SVT and cancer who are not at high-risk of bleeding, while more data on use of LMWH and DOACs are needed. Future studies of cancer-related SVT patients with high and low risk of bleeding are needed to address this important unmet need.

The most common anticoagulant therapies used in patients with cancer or MPNs were LMWH and VKA. While DOACs may be safe and effective in patients with MPNs, reliable estimates of outcomes are yet to be generated in this patient population.[29–31] Based on our systematic review, it seems that VKAs are suggested for management of MPN-related SVTs, given less evidence available on other anticoagulant types; more studies are required to ascertain efficacy and safety of LMWH, and more so for DOACs, in patients with MPN.[32] Risk of bleeding remained low using VKA and LMWH in this patient population.

The use of DOACs was considerably infrequent compared to LMWH and VKA for patients with SVT and either cancer or MPN. DOACs are regarded as a common treatment strategy for managing cancer-associated VTEs.[33] All randomized trials investigating the effects of DOACs for the management of cancer-associated VTE have excluded SVT patients except the ADAM-VTE trial.[34] This might be explained by the different natural history and prognosis of SVTs compared to lower extremity DVT or PE in this patient population. However, the results of these trials comparing DOAC to LMWH for the management of cancer-associated VTE can be informative for the planning of future SVT studies. A recent systematic review and meta-analysis of 6 studies comparing DOACs and LMWHs for patients with cancer-associated VTE reported that patients receiving DAOCs had an approximately 33% relative risk reduction (risk ratio of 0.67) of recurrent VTE but a non-significant increase in risk of major bleeding (risk ratio of 1.17).[35] DOACs should be used with caution in patients at high risk of bleeding such as those with gastrointestinal or

genitourinary tract cancers.[36] Potential drug–drug interactions and patient preference are also considerations when starting DOACs for cancer-associated VTEs.

Patients with cancer who received an initial 6 months of therapeutic dose anticoagulation for VTE, and were given an additional 6 months of anticoagulation, are at a higher risk of major bleeding complications compared to those receiving placebo.[37] We found a two-fold increase in risk of clinically-relevant bleeding for patients with cancer and SVT receiving anticoagulant therapy compared to those who got no anticoagulation. Previous studies have also reported that the risk of major bleeding in patients with cancer receiving anticoagulation may be more frequent in patients with gastrointestinal or genitourinary cancers (particularly with DOACs), which constituted a large portion of our patient population's tumour type.[38] Interestingly, the risk of clinically-relevant bleeding complications seem to be reduced in patients with MPN receiving anticoagulant therapy. It is possible that anticoagulant therapy led to improve recanalization and avoidance of portal hypertension, potentially decreasing the risk of upper gastrointestinal esophageal major bleeding episodes. Nonetheless, careful assessment of the underlying risk of bleeding before initiation of anticoagulant therapy in patients with MPN and SVT is warranted.

We found no difference in overall mortality among patients with cancer or MPN and SVT receiving anticoagulant therapy or not. However, only a small case series study including 14 patients reported all-cause mortality of patients receiving anticoagulant therapy or not, and follow-up duration. Three studies reported on the incidence of all-cause mortality in patients with SVT and cancer (IRR: 0.71, 95% CI: 0.34-1.48). The lack of difference in risk of mortality between patients who received anticoagulant therapy or not may be partially due to the lack of significant reduction in recanalization, recurrent VTE, and SVT progression which have been suggested to be important potential predictors of mortality in patients with cirrhosis.[39] A recent individual patient

data meta-analysis in patients with SVTs (including some with cancer or MPN) found, through time-varying sensitivity analysis, that a subgroup of patients with SVT and receiving anticoagulation had a 4-time lower risk of all-cause mortality.[40] Our results were based on non-randomized, observational studies specifically including patients with cancer or MPN that mostly did not adjust for residual confounding and had an overall serious risk of bias. Hence, additional studies in these patient populations are desperately needed to address this important knowledge gap.

It is important to acknowledge the limitations of our systematic review. Many included studies did not report on dosing and duration of anticoagulant therapy. It must also be noted that some studies did not report the definition of the different bleeding outcomes. Lack of consistent reporting for bleeding, or if left to the discretion of the treating physician, can introduce bias in the overall bleeding incidence rate. Furthermore, there were no RCTs included in the review, possibly leading to bias due to potential difference in baseline patient characteristics resulting in confounding and differences in outcomes of patients who received anticoagulation and those who did not. Additionally, there was a high variability in the type of cancer, location of SVT, follow-up duration, and duration of anticoagulation given to patients which led to considerable heterogeneity for some of the pooled incidence rates. The number of event rates are also relatively low leading to imprecision and wide confidence intervals observed in some of the incidence rate ratios. RCTs on use of different anticoagulant therapies for the management of SVT in patients with cancer or MPNs could provide more precise and valid evidence to aid physicians' treatment decisions.

Conclusion

Anticoagulant therapy appears to increase the risk of clinically-relevant bleeding without decreasing the risk of vein recanalization, recurrent VTE, SVT progression/extension, or all-cause mortality, in patients with SVT and cancer. Anticoagulant therapy seems to decrease the risk the recurrent VTE without increasing the risk of clinically relevant bleeding in patients with MPN and SVT.

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Tables and Figures

Table 1. Features of this Review's Included Studies

Duration of Anticoagulation	# of Patients Who Did Not Receive Any Anticoagulation	SVT resolution	Vein recanalization	SVT progression	Bleeding	SVT recurrence	Mortality
Some for 6-12 months; others long term	0					HR	
	0					N (%)	N (%)
6 months: n=3 Long term: n=23	0			N (%)	N (%)	N (%)	
	0	N (%)		N (%)		N (%)	N (%)
Median (Range): 26 months (1-62 months) Indefinite anticoagulation: n=6	0	N (%)	Probability		N (%)	Incidence in patient-years	N (%)
Median (SD): 6.65 months (4.03 months)	41				N (%), Cumulative Incidence, and HR	Cumulative Incidence and HR	N (%), Cumulative Incidence, and HR
	7	N (%)			N (%)	N (%)	
Mean (Range): 75 days (11–122 days)	7						N (%) and Survival Time

Was Chemotherapy Treatment Given? (Yes/No)	Site of SVT, n (%)	Clinical vs. Incidental SVT	AC Control Group Present? (Yes/No)	AC vs. No-AC Groups Separated by Baseline Parameters (Subgroups)	# of Patients Receiving Anticoagulation	Type of Anticoagulant Received, n (%)
Yes		Mixed			63	VKA: 63 (100%)
Yes	PVT: 41 (67.2%) BCS: 20 (32.8%)	Mixed			61	
	BCS: 4 (17.4%) EHPVO: 11 (47.8%) Portal vein and at least 1 other vein: 8 (34.8%)	Mixed			23	VKA: 23 (100%)
Yes	PVT: 6 (60%) Mesenteric+splenic+portal vein thrombosis: 2 (20%) Splenic+portal vein thrombosis: 2 (20%)			Age, sex, type of cancer, type of SVT	10	VKA: 10 (100%)
Yes		Mixed			8	LMWH + VKA: 8 (100%)
Yes	Portal: 71 (79.6%) Mesenteric: 41 (31.1%) Suprahepatic: 17 (12.9%) Splenic Vein: 12 (9.1%) Multiple vein thrombosis: 36 (27.3%)	Mixed	Yes	Age, sex, type of cancer, history of VTE, cancer therapy, incidentally diagnosed SVT	91	Parenteral therapy: 61 (67.0%) VKA: 30 (33.0%)
Yes	Portal vein: 11 (61%) Superior mesenteric vein: 9 (50%) Inferior mesenteric vein: 1 (6%) Splenic Vein: 3 (17%) Inferior vena cava: 1 (6%) Other: 2 (11%) Multiple visceral sites of thrombosis: 8 (44%) Multiple visceral sites or concurrent PE/DVT: 10 (55%)	Incidental	Yes		11	Either LMWH or VKA: 11 (100%)
		Mixed	Yes		6	LMWH: 5 (83.3%) LMWH + VKA: 1 (16.7%)

Population	Follow-up Duration	# of Patients with SVTs and Cancer/MPN	Age	Male, n (%)	Cancer Type, n (%)	Does Study Report History of VTE? (Yes/No)
MPN and SVT	Median (Range): 1.7 years (1-37 months)	63				
MPN and SVT	Median (Range): 11 years (0.8-34 years)	61	Median (Range): 43 years (15-80 years)	23 (37.7%)	PV: 42 (69%) ET: 15 (25%) PMF: 4 (6%)	
MPN and SVT		23		12 (52.2%)	PV: 8 (34.8%) ET: 8 (34.8%) PMF: 2 (8.7%) Post-ET MF: 2 (8.7%) Not reported: 3 (13.0%)	Yes
MPN and SVT		10	Group 1 (n=4): Median (Range): 47 years (35-55 years) Group 2 (n=6): Median (Range): 60 years (45-65 years)	2 (20%)	PV: 3 (30%) ET: 1 (10%) PMF: 5 (50%) PNH: 1 (10%)	
MPN and SVT	Median (Range): 164 months (88-215 months)	8	Median (Range): 46 years (17-78 years)		PV: 3 (37.5%) ET: 2 (25%) PMF: 1 (12.5%) Unclassified MPN: 2 (25%)	
Solid cancer and SVT	Median (IQR): 12 months (4.8 to 12 months)	132	Median (IQR): 61.0 years (52.0, 70.5 years)	89 (67.4%)	Gastrointestinal: 34 (25.8%) Genitourinary: 28 (21.2%) Hepatobiliary and pancreatic: 76 (57.6%) Other sites: 8 (6.1%)	Yes
GI cancer and SVT	Mean (95%CI): 53 months (37-54)	18	Median (Range): 64.5 years (47–85 years)	10 (56%)	Colorectal cancer (St.II/III): 1 (6%) Colorectal cancer (St.IV): 5 (28%) Advanced (St.III&IV pancreatic cancer): 10 (56%) Biliary tract cancer: 1 (6%) Hepatocellular cancer: 1 (6%)	
Primary or secondary liver malignancy and SVT	Mean (Range) for anticoagulation group: 291 days (22–981 days) Mean (Range) for no anticoagulation group: 90 days (6–219 days)	13				

SVT resolution	Vein recanalization	SVT progression	Bleeding	SVT recurrence	Mortality
	N (%)	N (%)		N (%)	N (%)
N (%)			N (%)	N (%)	
		N (%)			HR
			N (%) and HR		HR and Survival Time
			N (%)	N (%)	N (%)
				Incidence Rate and OR	
			N (%) and Incidence Rate	N (%) and Incidence Rate	
			N (%)	N (%)	
			N (%)	N (%)	

First Author's Last Name, Publication Year	Abstract/Full text	Design
DeStefano, 2019[41]	Abstract	Retrospective Cohort
Debureaux, 2019[42]	Abstract	Retrospective Cohort
Danaee, 2016[43]	Abstract	Retrospective Cohort
Giordano, 2018[44]	Abstract	Case series
Rupoli, 2016[45]	Abstract	Retrospective Cohort
Valeriani, 2021[46]	Full text	Prospective registry
Bozas, 2012[19]	Full text	Retrospective Cohort
Sule, 2018[47]	Full text	Retrospective Cohort

Clinical vs. Incidental SVT	AC Control Group Present? (Yes/No)	AC vs. No-AC Groups Separated by Baseline Parameters (Subgroups)	# of Patients Receiving Anticoagulation	Type of Anticoagulant Received, n (%)	Duration of Anticoagulation	# of Patients Who Did Not Receive Any Anticoagulation
Mixed	Yes		5			10
Mixed	Yes	Age, sex, type of SVT, incidentally detected VTE	4	LMWH + Rivaroxaban: 1 (25%) Rivaroxaban: 1 (25%) VKA: 2 (50%)	LMWH+Rivaroxaban: 6 months Rivaroxaban: 12 months VKA: 6 months	6
Incidental	Yes		12	LMWH: 7 (58.3%) VKA: 5 (41.7%)	Mean: 7.8 months	39
Mixed	Yes		51	LMWH: 37 (72.5%) VKA: 11 (21.6%) Other anticoagulants (e.g. fondaparinux): 3 (5.9%)		71
Mixed	Yes		12	VKA: 12 (100%)		2
	Yes		457	Heparin: 149 (32.6%) VKA: 289 (63.2%) Heparin + VKA: 19 (4.2%)		61
Mixed	Yes		166	LMWH + VKA: 153 (92.2%) Heparin: 10 (6.0%) DOAC: 3 (1.8%)	Indefinite VKA: n=136 (88.9%) Median (Range): 3.5 years (8 months-15.8 years) VKA discontinued: 17 (9.3%) Median (Range): 2 years (1 month-6.2 years)	15
	Yes		48	LMWH: 12 (25%) VKA: 25 (52.1%) DOAC: 12 (25%) Fondaparinux: 1 (2.1%)	Median (Range): 23.9 months (1.7-77.6 months)	16
Clinical	Yes	Age, sex, type of SVT, number of usual site VTE, type of AC	4	VKA: 4 (100%) Heparin: 1 (25%)		3

# of Patients with SVTs and Cancer/MPN	Age	Male, n (%)	Cancer Type, n (%)	Does Study Report History of VTE? (Yes/No)	Was Chemotherapy Treatment Given? (Yes/No)	Site of SVT, n (%)
15	Mean (SD): 61 years (11.9 years)	8 (53.3%)	Pancreatic cancer: 6 (40%) Colon cancer: 3 (20%) Not reported: 6 (40%)			
10	Median (Range): 64 years (39-87 years)	6 (60%)	Right colon: 1 (10.0%) Left colon: 1 (10.0%) Rectum: 8 (80.0%) Multiple sites: 0 (0.0%)		Yes	Portal/Mesenteric vein thrombosis: 4 (40%) Intrahepatic branches: 6 (60%)
51	Mean: 60.3 years	42 (82%)	HCC: 51 (100%)		Yes	Right PVT: 19 (37%) Left PVT: 14 (27%) Main PVT: 8 (16%) Multi-involvement: 10 (20%)
122	Mean: 63.1 years	120 (98.4%)	Advanced pancraetic cancer: 122 (100%)		Yes	
14	Mean: 47.3 years	3 (21.4%)	PV: 5 ET: 3 PMF: 0 Latent/Unclassifiable: 6	Yes	Yes	Budd Chiari: 3 (21.4%) PVT only: 7 (50%) PVT +/- Splenic Vein +/- Superior Mesenteric Vein: 4 (28.6%)
518	Median (Range): 44 years (12-90 years)	195 (37.6%)	PV: 192 (37.1%) ET: 178 (34.4%) Overt PMF: 68 (13.1%) MPN-unclassified: 55 (10.6%) Pre-PMF: 20 (3.9%) Post-PV MF: 4 (0.8%) Post-ET MF: 1 (0.2%)		Yes	PVT: 349 (67.4%) Splenic Vein Thrombosis: 152 (29.3%) Mesenteric vein thrombosis: 126 (24.3%) BCS: 129 (24.9%)
181	Median (Range): 48 years (29–74 years)	63 (34.8%)	PV: 67 (37.0%) ET: 67 (37.0%) PMF: 47 (26.0%)	Yes	Yes	Hepatic vein thrombosis: 31 (17.1%) PVT: 109 (60.3%) Mesenteric vein thrombosis: 18 (9.9%) Splenic Vein Thrombosis: 23 (12.7%)
64	Median (Range): 45 years (18-89 years)	18 (28%)	PV: 29 (45%) ET: 14 (22%) PMF: 8 (13%) Post-ET/PV MF: 5 (8%) Pre-PMF: 2 (3%) MDS/MPN, unclassifiable: 1 (2%) MPN unclassifiable: 5 (8%)		Yes	"BCS: 23 (36%) PVT: 44 (69%) Other: 23 (36%) Splenic Vein Thrombosis: 13 (20%) Superior mesenteric vein thrombosis: 9 (14%) IVC: 1 (2%)"
7	Mean (SD): 43.6 years (5.4 years)	2 (28.6%)	PV: 7 (100%)		Yes	PVT: 5 (71.4%) Superior mesenteric vein thrombosis: 5 (71.4%) Splenic Vein Thrombosis: 4 (57.1%) Hepatic vein thrombosis: 3 (42.9%)

First Author's Last Name, Publication Year	Abstract/Full text	Design	Population	Follow-up Duration
Acuna-Villaorduna, 2019[20]	Full text	Retrospective Cohort	Pancreatic or colon cancer, and SVT	Mean (SD): 12 months (3 months)
Kim, 2020[18]	Full text	Retrospective Cohort	Colorectal cancer and post-operative PMVT	Average reported time to events: 6 months Total observation time per patient: 5-8 years
Mahmoudi, 2019[48]	Full text	Retrospective Cohort	HCC and PVT	Mean: 18.4 months
Afzal, 2020[49]	Full text	Retrospective Cohort	Stage II, III or IV pancreatic adenocarcinoma and SVT	Average: 1 year
Greenfield, 2018[50]	Full text	Case series	MPN and SVT	Median (Range): 88.5 months (8–211 months)
Sant'Antonio, 2020[51]	Full text	Retrospective Cohort	MPN and SVT	Median (Range): 89.9 months (0.5-430 months)
DeStefano, 2016[52]	Full text	Retrospective Cohort	MPN and SVT	Median (Range): 3.2 years (1 month - 15.8 years) Total overall observation time: 735 years
Tremblay, 2020[53]	Full text	Retrospective cohort	MPN and SVT	Median: 61 months
Muller, 1993[54]	Full text	Case series	MPN and SVT	

Acronyms: VTE = Venous Thromboembolism; AC = Anticoagulation; MPN = Myeloproliferative Neoplasm; SVT = Splanchnic Vein Thrombosis; VKA = Vitamin K Antagonist; HR = Hazard Ratio; PV = Polycythemia Vera; ET = Essential Thrombocythemia; PMF = Primary Myelofibrosis; PVT = Portal Vein Thrombosis; BCS = Budd-Chiari Syndrome; MF = Myelofibrosis; EHPVO = Extrahepatic Portal Vein Obstruction; PNH = Paroxysmal Nocturnal Hemoglobinuria; LMWH = Low Molecular Weight Heparin; IQR = Interquartile Range; GI = Gastrointestinal; CI = Confidence Interval; St. = Stage; DVT = Deep Vein Thrombosis; PE = Pulmonary Embolism; SD = Standard Deviation; PMVT = Portomesenteric Vein Thrombosis; HCC = Hepatocellular Carcinoma; OR = Odds Ratio; MDS = Myelodysplastic Syndrome; IVC = Inferior Vena Cava.

Table 2. Clinical and radiological outcomes of interest in patients with cancer and SVT who received anticoagulation. SVT = Splanchnic Vein Thrombosis; VTE = Venous Thromboembolism; CI = Confidence Interval.

Clinical/Radiological outcome	**Number of events in individuals who received anticoagulation**	**Number of studies**	**I^2**	**Incidence rate (95% CI), per 100 patient years**
Vein Recanalization	6/14	3	0%	15.61 (7.01-34.75)
VTE Recurrence	7/111	4	0%	5.09 (2.49-10.41)
SVT Progression/Extension	6/17	2	0%	29.83 (13.83-64.36)
Clinically-Relevant Bleeding	21/169	5	77%	7.81 (2.57-23.69)
All-Cause Mortality	41/102	3	32%	45.48 (27.05-76.46)

Table 3. Clinical and radiological outcomes of interest in patients with cancer and SVT who did not receive anticoagulation. SVT = Splanchnic Vein Thrombosis; VTE = Venous Thromboembolism; CI = Confidence Interval.

Clinical/Radiological outcome	**Number of events in individuals who did not receive anticoagulation**	**Number of studies**	**I^2**	**Incidence rate (95% CI), per 100 patient years**
Vein Recanalization	7/16	2	0%	17.56 (8.37-36.83)
VTE Recurrence	6/64	4	14%	7.47 (3.28-16.97)
SVT Progression/Extension	21/49	2	0%	30.46 (19.86-46.72)
Clinically-Relevant Bleeding	9/125	4	37%	4.76 (1.45-15.65)
All-Cause Mortality	24/58	3	82%	61.11 (15.90-234.87)

Table 4. Clinical and radiological outcomes of interest in patients with cancer and SVT who received anticoagulation and those that did not. SVT = Splanchnic Vein Thrombosis; VTE = Venous Thromboembolism; CI = Confidence Interval.

Clinical/ Radiological outcome	Number of events in individuals who received anticoagulation	Number of events in individuals who did not receive anticoagulation	Number of studies	I^2	Incidence rate ratio (95% CI)
Vein Recanalization	5/9	7/16	2	0%	1.15 (0.36-3.65)
VTE Recurrence	7/111	6/64	4	0%	0.86 (0.29-2.55)
SVT Progression/Extension	6/17	21/49	2	0%	0.95 (0.39-2.28)
Clinically-Relevant Bleeding	18/157	9/125	4	0%	2.22 (1.02-4.86)
All-Cause Mortality	41/102	24/58	3	0%	0.71 (0.34-1.48)

Table 5. Clinical and radiological outcomes of interest in patients with MPN and SVT who received anticoagulation. MPN = Myeloproliferative Neoplasm; SVT = Splanchnic Vein Thrombosis; VTE = Venous Thromboembolism; CI = Confidence Interval.

Clinical/Radiological outcome	**Number of events in individuals who received anticoagulation**	**Number of studies**	**I^2**	**Incidence rate (95% CI), per 100 patient years**
Vein Recanalization		0		
VTE Recurrence	48/515	4	80%	2.19 (1.14-4.23)
SVT Progression/Extension		0		
Clinically-Relevant Bleeding	27/226	3	47%	3.11 (1.80-5.38)
All-Cause Mortality	0/12	1		0.00 (0.04-9.03)

Table 6. Clinical and radiological outcomes of interest in patients with MPN and SVT who did not receive anticoagulation. MPN = Myeloproliferative Neoplasm; SVT = Splanchnic Vein Thrombosis; VTE = Venous Thromboembolism; CI = Confidence Interval.

Clinical/Radiological outcome	**Number of events in individuals who did not receive anticoagulation**	**Number of studies**	**I^2**	**Incidence rate (95% CI), per 100 patient years**
Vein Recanalization		0		
VTE Recurrence	48/383*	4	75%	4.39 (2.15-9.00)
SVT Progression/Extension		0		
Clinically-Relevant Bleeding	12/33	3	45%	5.98 (2.40-14.94)
All-Cause Mortality	0/2	1		0.00 (0.21-54.19)

*Note: The total number of patients who did not receive anticoagulation includes those who did not receive any anticoagulation and those on VKA who were off of it for some time.

Table 7. Clinical and radiological outcomes of interest in patients with MPN and SVT who received anticoagulation and those that did not. MPN = Myeloproliferative Neoplasm; SVT = Splanchnic Vein Thrombosis; VTE = Venous Thromboembolism; CI = Confidence Interval.

Clinical/ Radiological outcome	Number of events in individuals who received anticoagulation	Number of events in individuals who did not receive anticoagulation	Number of studies	I^2	Incidence rate ratio (95% CI)
Vein Recanalization			0		
VTE Recurrence	48/515	48/383*	4	0%	0.49 (0.32-0.74)
SVT Progression/Extension			0		
Clinically-Relevant Bleeding	27/226	12/33	3	0%	0.53 (0.26-1.07)
All-Cause Mortality	0/12	0/2	1		0.17 (0.00-8.40)

*Note: The total number of patients who did not receive anticoagulation includes those who did not receive any anticoagulation and those on VKA who were off of it for some time.

Study Flow Diagram

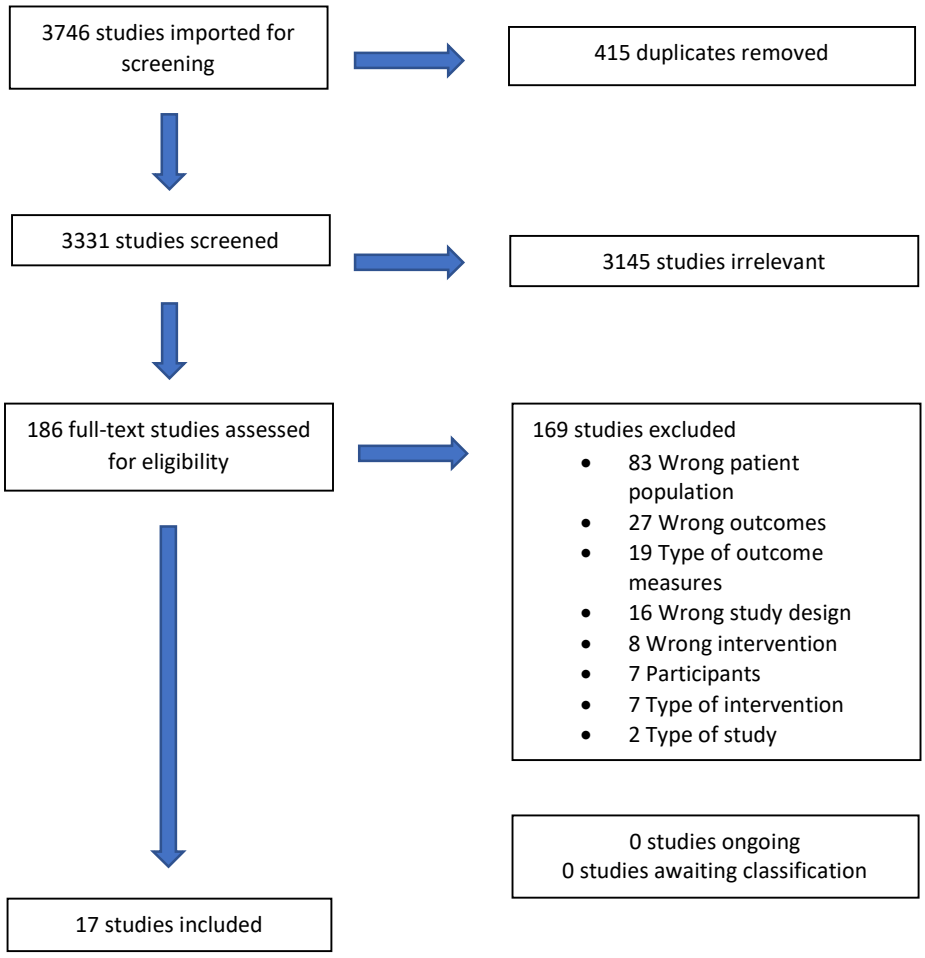

Figure 1. PRISMA Flow Diagram.

Outcomes in Patients with Cancer or MPN

Patients with cancer and SVT

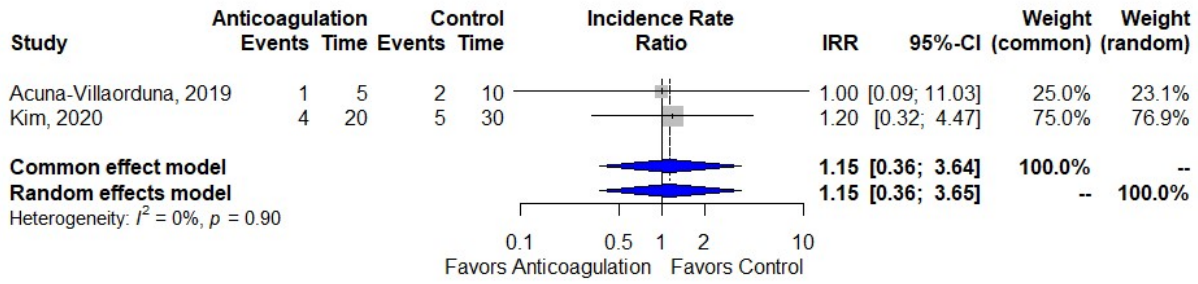

Figure 2. Forest plot of vein recanalization in patients with cancer and splanchnic vein thrombosis (SVT) who received anticoagulation and those who did not. IRR = Incidence Rate Ratio; CI = Confidence Interval.

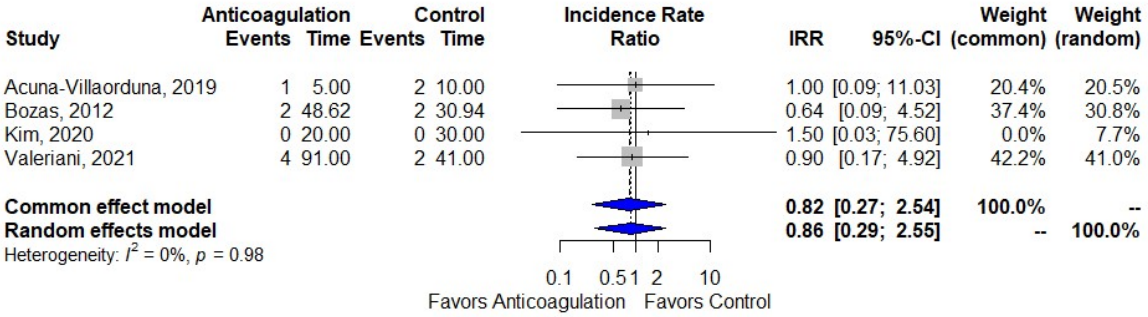

Figure 3. Forest plot of venous thromboembolism recurrence in patients with cancer and splanchnic vein thrombosis (SVT) who received anticoagulation and those who did not. IRR = Incidence Rate Ratio; CI = Confidence Interval.

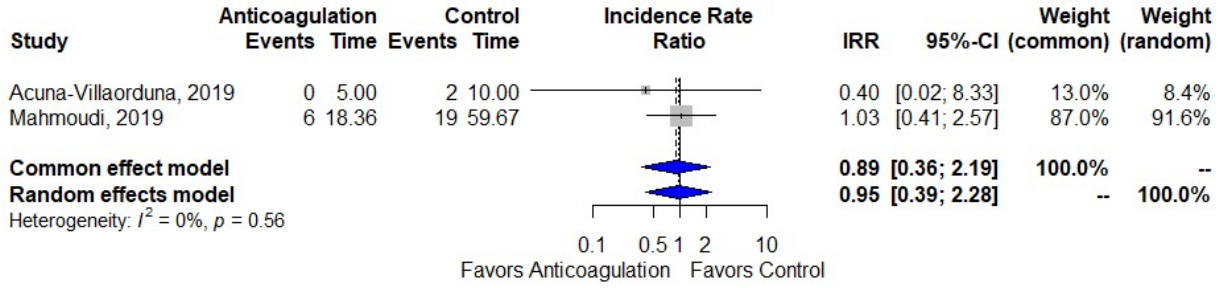

Figure 4. Forest plot of splanchnic vein thrombosis (SVT) progression/extension in patients with cancer and SVT who received anticoagulation and those who did not. IRR = Incidence Rate Ratio; CI = Confidence Interval.

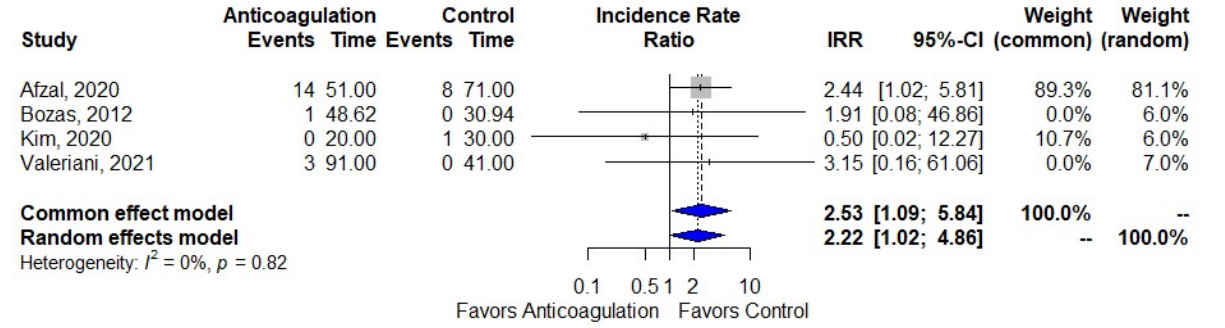

Figure 5. Forest plot of clinically-relevant bleeding in patients with cancer and splanchnic vein thrombosis (SVT) who received anticoagulation and those who did not. IRR = Incidence Rate Ratio; CI = Confidence Interval.

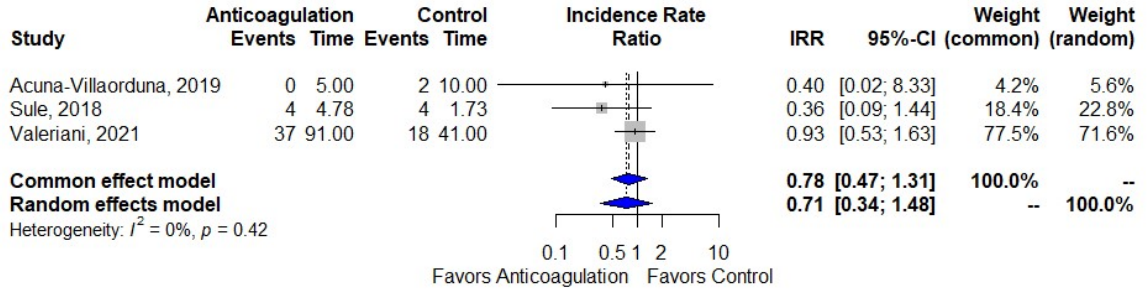

Figure 6. Forest plot of all-cause mortality in patients with cancer and splanchnic vein thrombosis (SVT) who received anticoagulation and those who did not. IRR = Incidence Rate Ratio; CI = Confidence Interval.

Patients with MPN and SVT

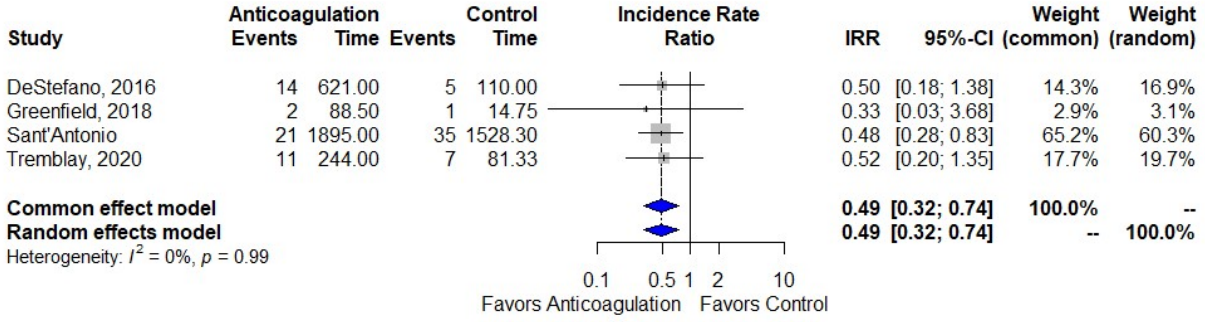

Figure 7. Forest plot of venous thromboembolism recurrence in patients with myeloproliferative neoplasm (MPN) and splanchnic vein thrombosis (SVT) who received anticoagulation and those who did not. IRR = Incidence Rate Ratio; CI = Confidence Interval.

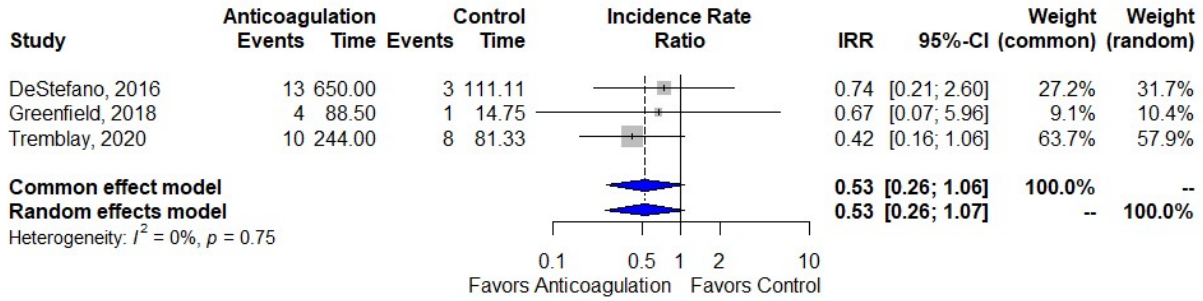

Figure 8. Forest plot of clinically-relevant bleeding in patients with myeloproliferative neoplasm (MPN) and splanchnic vein thrombosis (SVT) who received anticoagulation and those who did not. IRR = Incidence Rate Ratio; CI = Confidence Interval.

Risk of Bias Assessments

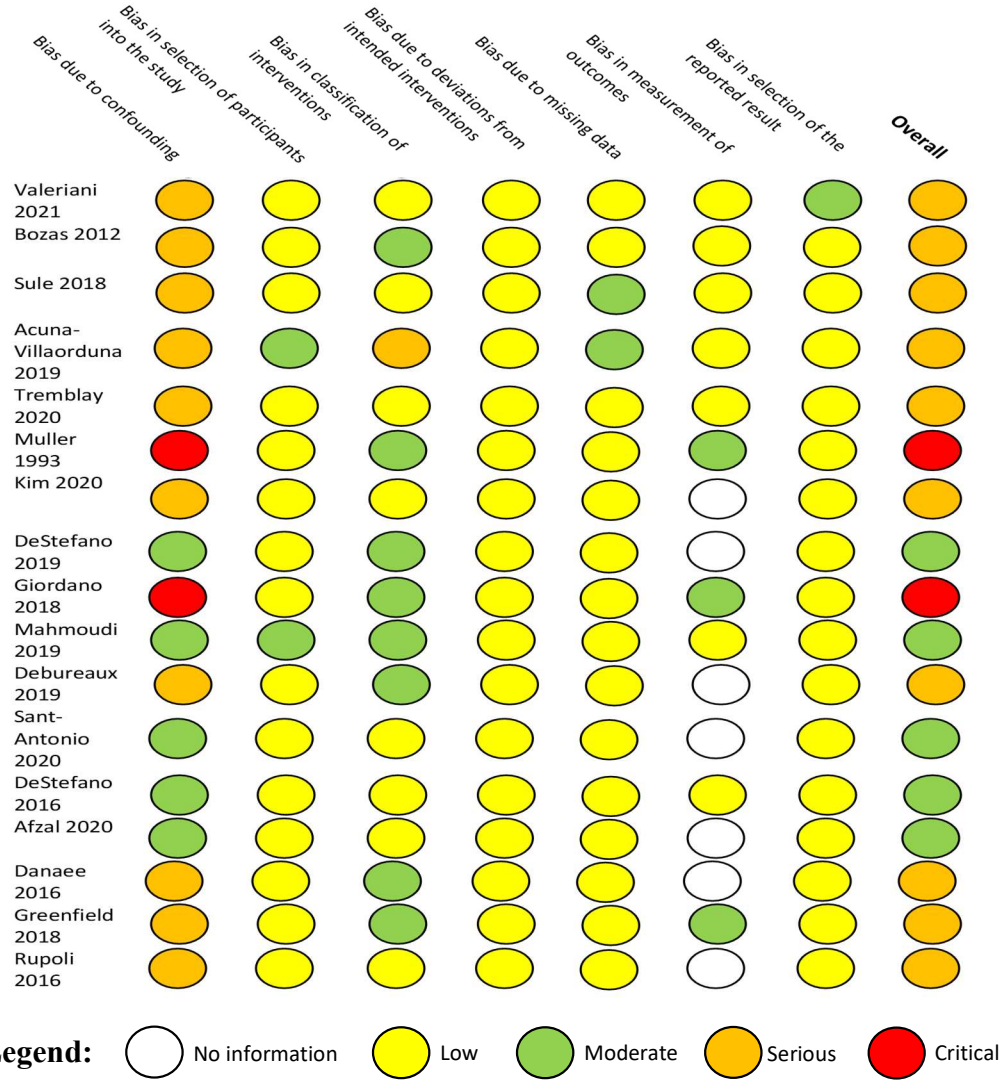

Figure 9. Risk of Bias assessments for 17 included studies. ROBINS-I was used to describe the biases in observational studies. The legend shows colour coding for the degree of bias represented. 7 domain components and an overall bias category are presented for each study.

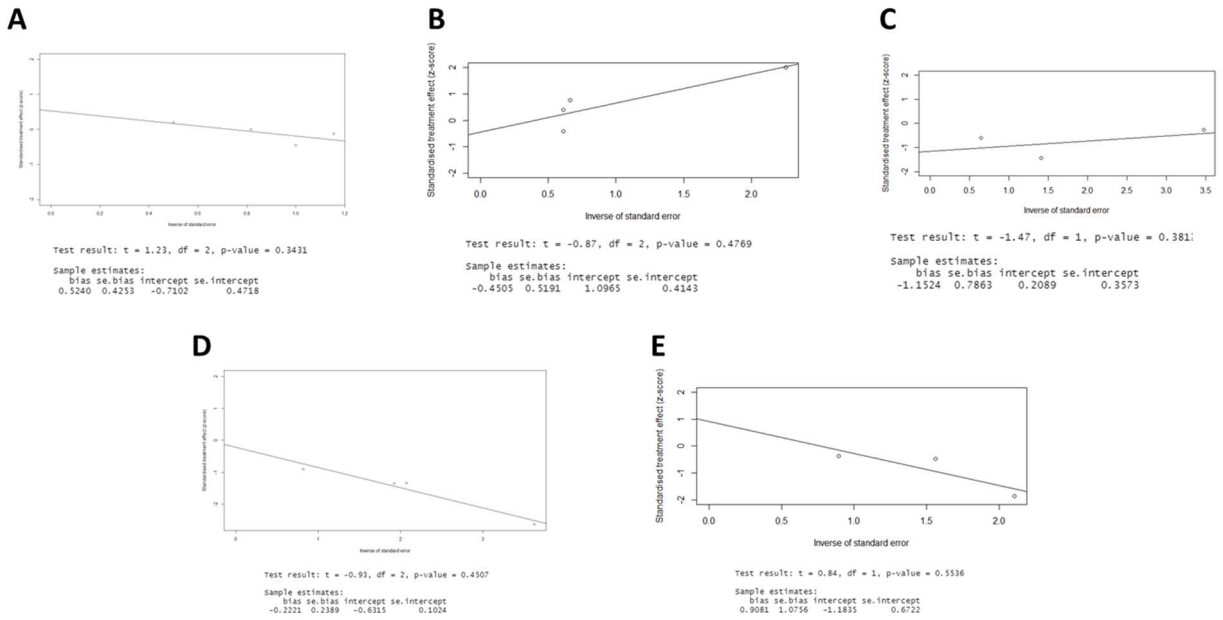

Figure 10. Egger's test for detecting evidence of publication bias using weighted linear regression of study treatment effect on its standard error. A = VTE recurrence in patients with cancer; B = Clinically-relevant bleeding in patients with cancer; C = All-cause mortality in patients with cancer; D = VTE recurrence in patients with myeloproliferative neoplasm (MPN); E = Clinically-relevant bleeding in patients with myeloproliferative neoplasm (MPN).

3. Delphi Survey of Canadian Physicians to Determine Optimal Anticoagulant Treatment Approaches for Patients with Cancer and Splanchnic Venous Thrombosis

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Keywords: Venous Thromboembolism; Splanchnic Circulation; Anticoagulants; Neoplasms; Delphi Survey.

Disclosures and/or Conflicts of Interest: AZ, AD, and MC do not have any conflicts of interest to disclose.

Abstract

Background: Cancer and myeloproliferative neoplasm (MPN) are both associated with a greater risk of venous thromboembolism (VTE), including atypical site splanchnic vein thromboses (SVT). Anticoagulation is often recommended for the management of SVTs in patients with cancer or MPN. Anticoagulant therapy seems to be associated with a higher risk of clinically-relevant bleeding and a non-significantly lower risk of recurrent VTE in patients with cancer and SVTs. For patients with SVT and MPN, anticoagulation is associated with lower risks of both recurrent VTE and clinically-relevant bleeding.

Aim: To do a survey of Canadian practices on management of patients with SVTs and cancer or MPN.

Methods: A 19-question online survey was developed on LimeSurvey and distributed to members of the Canadian Venous Thromboembolism Research Network (CanVECTOR), Thrombosis Canada, and Canadian Hematology Society. Responses were collected over 3 months and tallied to assess for consensus through coefficients of variance less than 0.30.

Results: A total of 45 clinicians completed the survey. Twenty-five respondents (55.6%) have practiced for more than 10 years. 40 (88.9%) were hematologists and 31 (69%) practiced in academic settings. A large majority of respondents felt that both low molecular weight heparins (LMWH) and direct oral anticoagulants (DOACs) were safe and effective for the management of SVT in patients with cancer or MPN. Overall, 35 (80%) respondents reported that randomized trials comparing a DOAC to a LMWH are needed in these populations. Only 25 (55.5%) respondents were comfortable with a placebo-controlled trial and 18 (72%) reported that an absolute risk reduction of 5% in recurrent VTE would be the minimal clinically important

difference (MCID). The responses on the MCID required for the rate of recurrent VTE for a trial comparing two different types of anticoagulants (e.g., DOAC vs. LMWH) were more heterogenous in patients with MPN and SVT, but 50% of respondents reported that a difference of 1% in clinically-important bleeding in this population would lead to change in clinical practice.

Conclusion: Canadian physicians seem to agree on most approaches when managing patients with SVT and cancer or MPN. Randomized controlled trials comparing different anticoagulant therapies are needed. Most respondents favored a trial comparing DOACs to LMWHs.

Introduction

Patients with cancer or myeloproliferative neoplasm (MPN) are at risk of developing venous thromboembolisms (VTE) including atypical site thrombosis such as splanchnic venous thromboses (SVTs).[28,55] SVTs include thrombosis in the hepatic, splenic, portal, and mesenteric veins. These thromboses require immediate medical attention as they can lead to bleeding, portal hypertension, Budd-Chiari syndrome, and/or death.[56] The prevalence of cancer-related SVT is relatively low in ambulatory patients with cancer, at about 1%,[57] while the incidence of SVT in patients with MPN is between 1% and 20%.[43] However, the best management strategies are not well established due to a paucity of data in these patient populations. Care of these patients has become multi-disciplinary, frequently including hematology, hepatology, and interventional radiology.[1] The choice to initiate anticoagulant therapy as well as which types and doses are important consideration for clinicians managing these patients.

We previously completed a systematic review and meta-analysis of the available evidence for the management of SVTs using anticoagulant therapy in patients with cancer or MPN. Low molecular weight heparins (LMWH) and vitamin K antagonists (VKAs) were the most common anticoagulants prescribed for patients with SVT and cancer or MPN, respectively. Direct oral anticoagulants (DOACs) were also investigated in these patient populations.[28] To avoid morbidity related to SVT, clinicians need to optimize the risk-benefit ratio of anticoagulant therapy and minimize the risks of recurrent VTE or clinically-relevant bleeding complications.[58]

Our systematic review reported that anticoagulant therapy appears to increase the risk of clinically-relevant bleeding without decreasing the risk of recurrent VTE in patients with cancer and SVT, while decreasing the risk of recurrent VTE without increasing the risk of clinically-relevant bleeding in patients with SVT and MPN. Following these results, we developed a survey

of practice for VTE specialists and fellows across Canada to establish consensus on current best practices for managing SVTs using anticoagulants in these patient populations.

Methods

The survey (https://tohthesisdelphisurvey.limesurvey.net/673278?lang=en) was distributed to a panel of physician or fellow thrombosis specialists (hematologists, VTE specialists, general internists, gastroenterologists/hepatologists, and radiologists), from the Canadian Venous Thromboembolism Research Network (CanVECTOR), Thrombosis Canada, and Canadian Hematology Society, through the Delphi method and via circulating a digital questionnaire using the online software LimeSurvey. The Delphi structure was used to develop consensus through receiving anonymous feedback on questions relating to management of SVTs with anticoagulant therapies in patients with cancer or MPN.[59,60] Collected responses were analyzed and the process was repeated until optimal consensus was reached.

Experts were asked to provide basic demographic information, on the risk/benefit ratio of anticoagulant therapies for the management of patients with cancer and MPN, and to select the optimal clinical management in specific cases to explore practice variation regarding anticoagulation practices for SVT. Experts were also asked about the feasibility of conducting a randomized clinical trial focusing on comparing: 1) anticoagulation therapy vs. placebo; and 2) different anticoagulation regimens for the management of SVT in patients with cancer or MPNs.[61] Participation of experts in the survey was voluntary and all responses were held anonymously. 2 emails were sent, separated by about 1 week, to remind participants of the survey.

Experts were provided with updated evidence on the clinical outcomes of the management of SVT in patients with cancer and MPN from our systematic review and meta-analysis. Pooled estimates on recurrent VTE and clinically-relevant bleeding for patients receiving anticoagulation (along with estimates based on the type of anticoagulant therapy) or not were provided. Survey responses were received and collated; since consensus was not reached after the first round of the Delphi process (using a cutoff coefficient of variance of 0.30), a second iteration was conducted, where participants could adjust their responses, and this process was repeated until consensus was reached.[62–65]. Based on their responses, a minimal clinically important difference (MCID) was derived to advise on any practice change for Canadian hematologists and VTE specialists on the treatment of SVTs in patients with cancer or MPN.

Within the survey, we specifically asked participants about the perceived risk of recurrent VTE and clinically-relevant bleeding using different anticoagulation regimens in patients with SVT and cancer or MPN, to assess feasibility of a randomized controlled trial (RCT) comparing outcomes after treatment with different anticoagulant therapies or placebo/observation, as well as risk reduction in recurrent VTE or increase in risk of clinically-relevant bleeding that could lead to change in clinical practice. We also included clinical vignettes to guide management of specific cases, determine potential for research of certain topics, and duration of anticoagulation. Our survey included 19 questions, including 4 demographic/background questions.

Descriptive analysis was done using Excel 2023 software (Microsoft Corporation, Redmond, DC, USA).

Results

Survey responses were collected over 3 months (between Nov. 2022 and Jan. 2023). A total of 45 experts responded to the survey. Overall, 43 (96%) respondents worked at an academic center and 2 (4%) had a community practice (**Fig. 1A**). 25 respondents (56%) had been in practice for >10 years, 7 (15%) for 5-10 years, and 13 (29%) for <5 years (**Fig. 1B**). In terms of main area of practice, 32 (71%) reported thrombosis as their main area of practice, 8 (18%) reported hematology, and 5 (11%) had expertise outside of either field (**Fig. 1C**). When asked about work time spent in research, 7 (16%) spent >75%, 13 (29%) spent about 50%, 11 (24%) spent about 25%, and for 14 (31%), research was not a main area of focus (**Fig. 1D**).

All respondents felt that anticoagulant therapy, specifically LMWH or DOACs, were effective for the management of SVT in patients with cancer or MPN. (**Fig. 2A**). A majority of respondents (89%) also felt that LMWH and DOAC were safe regarding the risk of clinically-relevant bleeding, while 5 (11%) reported that the risk was well-controlled with LMWH, but that the risk was higher with DOACs (**Fig. 2B**). Overall, 35 respondents (80%) were interested in participating in RCTs in these patient populations. A majority opted for a RCT comparing DOACs to LMWHs in patients with SVT and cancer (**Fig. 3A**). Furthermore, 25 (56%) respondents were comfortable to participate in a placebo-controlled RCT comparing anticoagulant therapy to placebo in patients with SVT and cancer or MPN (**Fig. 3B**).

The MCID on the absolute risk reduction in recurrent VTE (over a 12-month follow-up period) required to change clinical practice were explored for two hypothetical scenarios: 1) RCT comparing anticoagulant therapy to placebo in patients with SVT and cancer or MPN; and 2) RCT comparing different anticoagulant regimens in patients with SVT and cancer or MPN. In the first hypothetical scenario, the majority of respondents (18 (72%)) were comfortable with a

5% risk reduction, while 6 (24%) preferred a 2% reduction, and 1 (4%) a 7% reduction (**Fig. 4A**). A total of 20 participants did not provide a response. In the second hypothetical scenario, results were more heterogeneous. Overall, 15 (36%), 2 (5%), 12 (29%), 10 (24%), and 3 (7%) preferred a 0%, 1%, 2%, 3%, or 4% reduction, respectively (**Fig. 4B**). The MCID on the absolute risk increase in clinically-relevant bleeding (over a 12-month follow-up period) that would be reasonable to be change clinical practice and use a DOAC (i.e., oral medication) instead of LMWH (i.e., daily injections) was also determined and approximately half of the respondents found a 1% increase in this risk to be acceptable (**Fig. 5**). A total of 4 (9%), 2 (5%), 11 (25%), and 5 (11%) participants reported 0%, 0.5%, 2%, and 3%, respectively (**Fig. 5**). The coefficient of variations reached a consensus in experts' responses for the MCID on recurrent VTE in an RCT comparing anticoagulant therapy to placebo and for clinically-relevant bleeding in a trial comparing different anticoagulant regimens. Hence, a second iteration was not performed.

We also explored if the anticoagulant regimens would change in patients with SVT and cancer or MPN at high risk of bleeding, or with a diagnosis of incidental SVT (vs. symptomatic) along with duration of anticoagulation in these patient populations. In patients with symptomatic or incidental SVT at low risk of bleeding, the majority of respondents reported using therapeutic dosing of DOAC. The presence of symptoms or an incidental diagnosis did not seem to alter the type and dose of anticoagulant therapy. In patients with SVT and cancer or MPN at high risk of bleeding (liver cirrhosis and prior history of banded esophageal varices), the majority of respondents (55%) opted for therapeutic dosing of LMWH. Another 18% used LMWH to challenge the patient to anticoagulation followed by a transition to therapeutic DOAC if no bleeding complications were identified. Finally, respondents were asked to assess duration of anticoagulation for secondary prevention of recurrent events. A large majority of respondents

(82%) would discontinue anticoagulation after an SVT provoked by an additional risk factor (e.g., SVT post colorectal cancer resection), whereas the majority would continue indefinite anticoagulation therapy in patient with ongoing risk factors (e.g., polycythemia rubra vera with SVT at low risk of bleeding). However, dosing was more heterogeneous and 20% of respondents would consider a prophylactic dose of DOAC for secondary prevention in these patient populations.

Discussion

Our survey of practice of hematologists and experts in thrombosis reported an interest to perform RCTs in patients with SVT and cancer or MPN. Most respondents were favorable to a RCT comparing LMWH to DOAC for the management of SVT in these patient populations. The 1% increase in the risk of clinically-significant bleeding has been deemed to be acceptable and established as the MCID for future trials.

Current recommendations for managing SVTs in patients with cancer or MPN come mostly from small-scale observational studies or expert opinions. A clinical practice guideline on the management of SVT was published by the National Comprehensive Cancer Network (NCCN), making a weak recommendation for patients with cancer and acute SVTs to receive anticoagulant therapy if there are no contraindications to treatment.[22] The 2021 American Society of Hematology guidelines for prevention and treatment of VTE in patients with cancer makes a very weak conditional recommendation on treating SVTs with short-term (3-6 months) anticoagulation or observation.[10] Hence, there is a desperate need for level 1 evidence from RCTs to address this important unmet need.

Most of our respondents work in academic centers and have research experience and expertise in thrombosis medicine. Hence, they have the potential to properly inform the knowledge gap and feasibility of additional studies in this research area. We shared the results of our previous meta-analysis[66] to help guide the establishment of consensus-driven MCID for future RCTs in these patient populations. While our systematic review did not report a statistically significant benefit from anticoagulation for the risk of recurrence of VTE in patients with cancer and SVT, survey respondents believed that both LMWH and DOAC were effective treatment options, although 11% of respondents felt that the risk of bleeding was higher with DOACs. Hence, it is not surprising that respondents supported RCTs comparing LMWH to DOACs with a MCID of 1% in clinically-important bleeding. This is also consistent with previous literature in the management of cancer-associated VTE reporting that patients receiving DOACs might be at higher risk of developing major bleeding and clinically relevant non-major bleeding events as compared to those receiving LMWH.[35] The higher risk of bleeding complications seems to be particularly important in patients with gastrointestinal or genitourinary cancers.[67]

Interestingly, 56% of the respondents were open to a placebo-controlled RCT in patients with cancer or MPN. In our systematic review, anticoagulant therapy was associated with no statistically significant reduction of recurrent VTE and a significant increase in the risk of clinically-relevant bleeding in patients with SVT and cancer.[66] Hence, important gaps in optimal anticoagulant type, dosing, and timing may justify a placebo-controlled trial to confirm efficacy and safety in these patient populations.[28,68] Respondents established that the MCIDs in a placebo-controlled RCT would be a 5% reduction in risk of recurrent VTE to comfortably use anticoagulation in these patient populations.[66] Nonetheless, a majority of respondent preferred a trial comparing two different types of anticoagulant therapies, LMWHs and DOACs. Furthermore,

DOACs are not only frequently used in patients with cancer, but their use has also been increasingly reported in patients with MPN with growing evidence including a recent clinical guidance by the International Society on Thrombosis and Haemostasis (ISTH), but high-level evidence is still required.[11,68]

Clinical vignettes were an important part of our survey, presenting clinicians with specific patient scenarios when managing patients with SVT and either cancer or MPN. Most experts wanted to start full-dose DOAC for a patient with cancer and either symptomatic or incidental SVT and others to switch from 5-7 days of LMWH to full-dose DOAC, which is consistent with other published evidence.[10,11] Although the 2012 chest guidelines on antithrombotic therapy for VTE disease recommended using anticoagulation in patients with symptomatic SVT and no anticoagulation in those with incidental SVT[69], new clinical data has emerged since those recommendations for patients with cancer and those with incidental SVT, showing benefits of anticoagulants. Hence, the responses from the survey reporting no difference in treatment approach of patients with symptomatic or incidental SVT aligns with recommendations from the 2020 ISTH subcommittee on control of anticoagulation, in managing via either LMWHs (preferred in those with high bleeding risk) or DOACs.[11] The 2021 American Society of Hematology (ASH) guidelines on the management of VTE in patients with cancer suggested the use of short-term anticoagulation for patients with incidental PE or subsegmental PE, and short-term anticoagulation or observation for those with SVT.[10]

Most experts wanted to participate in an RCT between DOACs and LMWHs for patients with symptomatic SVT and cancer. Additionally, many experts suggested the use of 3-6 months of anticoagulation for managing symptomatic SVT in patients with cancer, as did the ISTH 2020 subcommittee.[11] The 2020 ASH guidelines for treatment of lower limb DVT and PE, suggested

using short-term anticoagulation for primary treatment of provoked (either transient or chronic risk factors) and unprovoked DVT/PE, over long-term anticoagulation (6-12 months).[70] In a patient with cancer, SVT, and a history of liver cirrhosis, who are at increased risk of bleeding, most experts went for a therapeutic dose of LMWH, potentially due to more data being available on the adverse outcome profile of the patients than for DOACs.[5] Use of therapeutic dose of DOACs is growing in patients with SVT and cancer or MPN as mentioned before but each unique patients need to undergo an assessment of risk of bleeding as clinicians decide which anticoagulant to provide.

Our study had strengths in that it asked a broad and national group of experts across Canada about practice patterns in managing patients with either cancer or MPN, and SVT. Most experts were exposed to research and can provide input into future study designs/topics needed in the field. Also, we covered a variety of clinical scenarios that can guide approach of clinicians. Consensus was high in most questions which strengthens the reliability of our derived MCIDs with few survey iterations and were supported by a thoroughly conducted systematic review and meta-analysis. Questions were left unanswered for a number of questions and better response rate can be encouraged by providing more context for questions for which there is little available clinical evidence or that are less known among clinicians. Definition of certain terms, such as recurrence of VTE or clinically-relevant bleeding, could have been provided to respondents for more clarity (for example ISTH definitions of major bleeding and clinically relevant non-major bleeding); these were inconsistently defined in studies included in our systematic review.[66]

Conclusion

Canadian physicians seem to agree on most anticoagulation-based treatment approaches for patients with either cancer or MPN, and SVT. Canadian experts have reported an interest to perform RCTs comparing LMWH to DOAC in patients with SVT and cancer or MPN. A 1% increase in the risk of clinically-relevant bleeding has been found to be acceptable and established as the MCID.

Tables and Figures

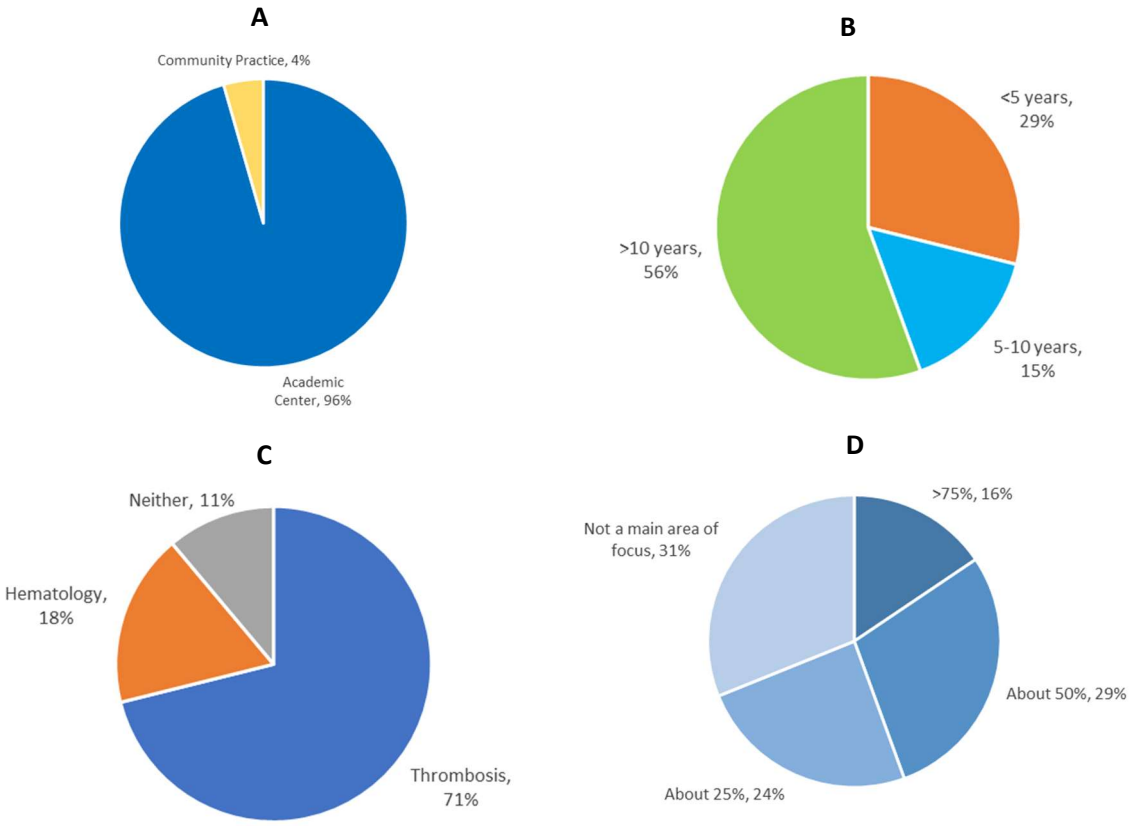

Figure 1: Demographic questions (N=45). **A)** Physicians' settings of practice; **B)** Years in practice; **C)** Main area of practice; **D)** Work time spent in research.

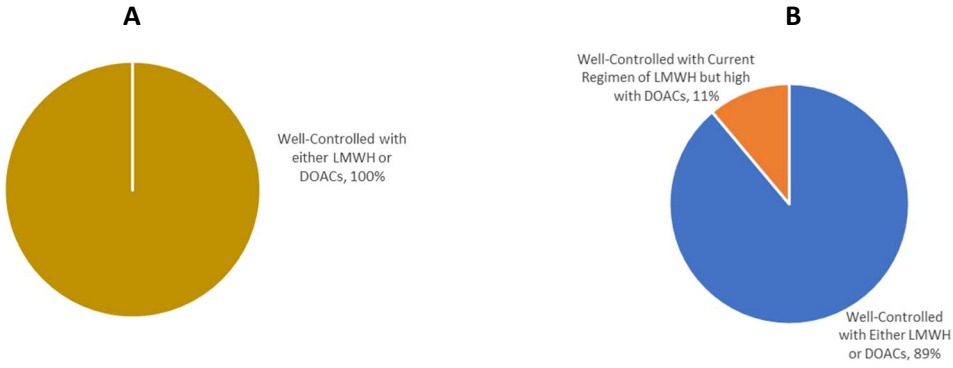

Figure 2: Perceived risk of **A)** recurrent VTE (N=44) and **B)** bleeding (N=45), in patients with cancer and SVT managed with low molecular weight heparins or direct oral anticoagulants.

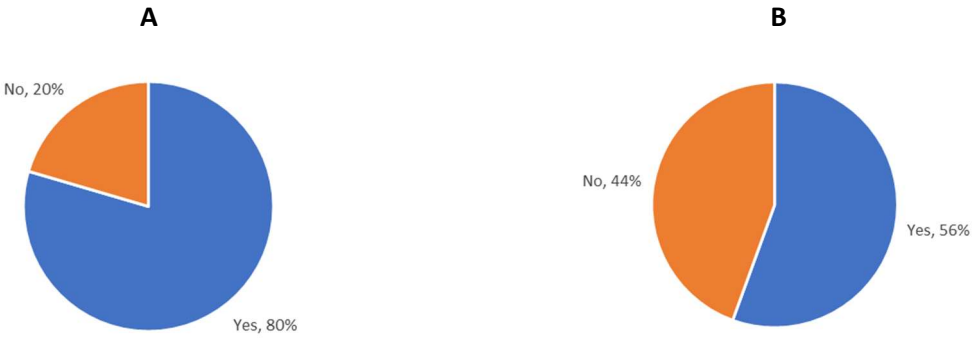

Figure 3: Openness to randomized controlled trials for comparing **A)** DOACs (direct oral anticoagulants) to LMWHs (low molecular weight heparins) in patients with cancer and splanchnic vein thromboses (SVTs) (N=44), and **B)** anticoagulation to placebo in patients with either cancer or myeloproliferative neoplasm (MPN), and SVTs (N=45).

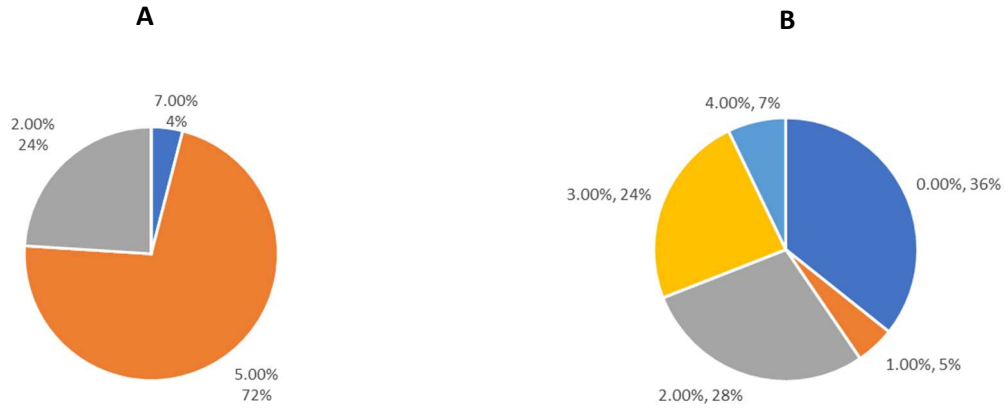

Figure 4: Absolute risk reduction in recurrent venous thromboembolism (VTE) over 12 months to lead to practice change after treatment with **A)** anticoagulants compared to placebo in patients with splanchnic vein thromboses (SVTs) (N=25) and cancer or myeloproliferative neoplasm (MPN), or **B)** different anticoagulants in patients with SVT and cancer or MPN (N=42).

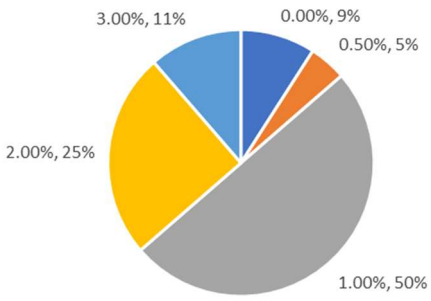

Figure 5: Acceptable increase in the overall risk of clinically-important bleeding over 12 months between two different anticoagulation regimens in the prevention of thrombotic complications in patients with splanchnic vein thromboses (SVT) and cancer or myeloproliferative neoplasms (MPN) (N=44).

4. Treatment of Splanchnic Venous Thrombosis in Patients with Cancer (SVT-CA) using LMWHs and DOACs: Protocol for a Pilot Randomized Controlled Trial

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Keywords: Venous Thromboembolism; Splanchnic Circulation; Anticoagulants; Neoplasms; Clinical Trial Proposal.

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Abstract

Background: Venous thromboembolism (VTE) is a common medical issue in patients with cancer. Guidelines based on observational studies and expert opinions suggest using short-term (3-6 months) anticoagulation with low molecular weight heparins (LMWH) or direct oral anticoagulants (DOAC) for management of acute splanchnic vein thrombosis (SVT) in patients with cancer. We are proposing the SVT-CA pilot trial to evaluate the feasibility of recruiting for comparison of managing acute symptomatic SVT in patients with cancer.

Methods: An open-label randomized non-inferiority trial is planned on comparing 6 months of anticoagulation using either DOACs or LMWHs in patients with acute symptomatic SVT and active cancer. The primary outcome will be the mean number of patients recruited per site per month. Secondary outcomes will include rate of eligibility, consent, retention, study completion, study procedure adherence, clinically-relevant bleeding (major and clinically-relevant non-major bleeding), recurrent VTE, and overall mortality. We will follow up with patients for 6 months and will have phone or in-person visits at months 1, 3, and 6. To conduct a non-inferiority trial with a non-inferiority margin of 1.0% (in clinically-relevant bleeding), the target sample size for the full-scale trial would be 13,096 patients with cancer. The convenient sample size for the pilot trial would be 360 across 3 Canadian Venous Thromboembolism and Outcomes Research (CanVECTOR) sites.

Discussion: There are no clinical trials to provide robust evidence on the management of patients with SVT and cancer. The SVT-CA trial will assess the feasibility of conducting a large-scale open-label non-inferiority Phase 3 trial randomizing patients with SVT and active cancer to DOAC or LMWH. We will also provide preliminary data on the clinical endpoints such as

clinically-relevant bleeding, recurrent VTE, vein recanalization, progression/extension, and all-cause mortality of patients undergoing anticoagulation.

Trial registration: This trial has not been registered on a platform yet.

Keywords: Venous thromboembolism; Splanchnic vein thrombosis; Cancer-associated thrombosis; Direct oral anticoagulants; Low molecular weight heparin; Pilot trial.

Introduction

Background

Venous thromboembolism (VTE) is a common medical condition with a global estimated incidence rate of 10-18 per 10,000 person-years and has been on the rise in the past decades.[71] This rate is higher in patients with cancer, with about 4-20% experiencing VTE in their lifetime[72] and increased risk of VTE recurrence while taking anticoagulant treatment.[72] One form of VTE, splanchnic venous thrombosis (SVT) (i.e. thrombosis in the abdominal veins that drain visceral organs (portal, mesenteric, splenic, and hepatic veins)), is also considerably associated with cancer. The prevalence of cancer in patients with SVT has been reported as high as 50%, although this varies based on the data source and tends to be heterogenous based on the location of the thrombosis and underlying cancer types.[28] These patients may have serious complications, with cumulative incidence rate of major bleeding of 3.6-4.4%, thrombotic events of 5.9-7.6%, and all-cause mortality reported as high as 39.5%.[5]

Optimal management of SVT in patients with cancer needs to be investigated. This has been challenging for clinicians as guidelines are rarely addressing the management of SVT in patients with cancer.[23,73]. The 2021 Chest guidelines on antithrombotic therapy for VTE disease suggest use of direct oral anticoagulants (DOACs) instead of low molecular weight heparins (LMWHs) for treatment in patients with acute cancer-associated VTE.[73] Guidance and guidelines from various scientific societies currently suggest using DOACs in patients with acute cancer-associated VTE and a low bleeding risk, and LMWH if patient's bleeding risk is high.[23,74,75] However, these recommendations are based on evidence from randomized controlled trials (RCTs) evaluating anticoagulation in patients with cancer-associated deep vein thrombosis

(DVT) of the lower extremities and/or pulmonary embolism (PE) and may not necessarily apply to patients with SVT and cancer.

While there are some recommendations for management of cancer-associated SVT, these are mostly weak, based on observational studies, or derived from recommendations in patients with cancer-associated VTE. The 2020 International Society on Thrombosis and Haemostasis (ISTH) subcommittee on the control of anticoagulation suggests using either LMWH or DOACs for patients with acute symptomatic SVT, with LMWH being preferred in patients with a high risk of bleeding or drug-drug interactions with DOACs.[11] Those with incidentally-detected SVT were recommended to receive similar treatment as patients with symptomatic SVT. For patients with Budd-Chiari Syndrome (BCS), indefinite anticoagulation with LMWH is recommended, or DOACs in those without liver dysfunction or contraindications. Experts then released the 2021 American Society of Hematology (ASH) guidelines for treatment of VTE in patients with cancer, providing a weak suggestion on using short-term (3-6 months) anticoagulation or observation for the management of patients with cancer-associated SVT, highlighting the need for RCTs in this patient population.[10] The other available clinical practice guideline on the management of patients with cancer and SVT was the 2022 National Comprehensive Cancer Network (NCCN), making a weak recommendation for anticoagulant therapy if there are no contraindications to treatment for these patients[22]. The benefits of anticoagulation and guidance on selection of anticoagulation type in this patient population remains mostly unknown highlighting clinical equipoise and the need for additional trials. Currently, clinicians need to individualize the care of each patient with SVT and cancer, balancing the risk of recurrent VTE and bleeding complications.

The potential benefits of different anticoagulant therapies are valid but is yet unquantified in managing patients with SVT and cancer.[11] This prompted us to investigate this topic via a systematic review and meta-analysis and survey from experts to learn about practice patterns for these populations. In our meta-analysis, we looked for important clinically-relevant outcomes reported in patients diagnosed with cancer-associated SVT, including risk of recurrent VTE, SVT progression/extension, splanchnic vein recanalization, clinically-relevant bleeding, and all-cause mortality. The systematic search identified retrospective cohorts or case series studies only; no randomized controlled trial previously investigated this research question. In comparison to no treatment, anticoagulant therapy in patients with cancer was associated with an increased risk of clinically-relevant bleeding and no change in the risk of VTE recurrence.[66] We then surveyed Canadian physicians with clinical and research expertise in hematology and thrombosis medicine, asking for their approaches to managing patients with cancer-associated SVT.[76] Most respondents reported they felt LMWH and DOACs are both effective and safe for managing SVTs in patients with cancer. Most agreed with the need for an RCT comparing LMWHs to DOACs, while only half favored a placebo-controlled trial of anticoagulation. We obtained a minimum clinically important difference (MCID) of 1% as the non-inferior margin in the risk of clinically-relevant bleeding between DOAC and LMWH to allow a change in practice.

In the absence of high-quality data, we designed a pilot trial to assess the feasibility of evaluating whether therapeutic dose of DOAC is non-inferior to LMWH monotherapy for the management of acute symptomatic SVT in patients with cancer.

Objectives

Pilot trial: To evaluate the feasibility of conducting a full-scale trial that will examine if the treatment of acute, symptomatic, cancer-associated SVT with DOACs is non-inferior to LMWH with respect to the risk of clinically-relevant bleeding over a 6-month exposure period.

Full-Scale trial: To evaluate if DOACs are non-inferior to LMWH with respect to the risk of clinically-relevant bleeding over a 6-month exposure period for the treatment of acute, symptomatic, cancer-associated SVT.

Methods

Study Design and Setting

Pilot trial: The SVT-CA pilot trial is a multicentre, randomized, open-label clinical trial designed to assess whether the SVT-CA protocol of therapeutic dose of DOACs compared to LMWHs for patients with acute, symptomatic objectively-diagnosed SVT and active cancer is feasible to move forward to a full-scale trial. The pilot investigation will also inform optimal design of the full-scale trial. If the pilot trial is feasible, its participants will be included in the full-scale trial.

Full-Scale trial: The full-scale trial will be a prospective, open-label, blinded end-point (PROBE) non-inferiority trial in Canadian tertiary care hematology-oncology centers. We will recruit patients with an acute symptomatic, objectively-diagnosed SVT. Patients will be randomized in a 1:1 fashion to receive either therapeutic dose DOACs or LMWHs for 6 months, during which we will conduct follow-up visits at 1, 3, and 6 months.

Intervention(s) and Comparator(s)

We will compare clinical outcomes in patients who will receive either DOACs or LMWHs for the treatment of their symptomatic SVT. Patients randomized to the DOAC group will receive either: 1) apixaban 10 mg twice daily per os (PO) for 1 week followed by 5 mg twice daily PO, 2) rivaroxaban 15 mg twice daily PO for 3 weeks followed by a daily dose of 20 mg PO, or 3) edoxaban 60 mg daily PO after an initial 5-day treatment with therapeutic dose of LMWH.

Patients randomized to the LMWH group will receive either: 1) dalteparin 200 U/kg daily for the first month then continue at 150 U/kg daily, 2) tinzaparin 175 IU/kg daily, or 3) enoxaparin 1 mg/kg twice daily.

Patients in both arms will be evaluated at local study sites and compliance with study procedures will be recorded. Patients will receive therapeutic anticoagulation for 6 months. The study intervention's dose may be changed at the discretion of the responsible clinician, although any deviations from the trial protocol will be documented.

Study Population

All adult patients with active cancer with a recently identified symptomatic SVT (within 5 days of potential enrollment) will be screened for study participation. Patients with symptomatic portal, hepatic, splenic, or mesenteric vein thrombosis will be eligible. Those who meet all inclusion criteria and provide informed consent will be recruited in the trial. Demographic and baseline data will be collected on case report forms. These include VTE risk factors, type/stage of cancer, anti-cancer treatments, clinical symptoms of SVT, location and

extent of SVT, imaging diagnosis of SVT (using computed tomography (CT), magnetic resonance imaging (MRI), or doppler ultrasound; endoscopic or surgical procedures will also be recorded), and blood/urine laboratory work.

Eligibility Criteria

The following criteria will be used to screen candidates for this trial.

Inclusion criteria:

- 18 years or older.
- Active cancer, defined by the Haemostasis and Malignancy Scientific and Standardization Committee (SSC) of the ISTH as "cancer diagnosed within the previous six months, recurrent, regionally advanced or metastatic cancer, cancer for which treatment had been administered within six months, or hematological cancer that is not in complete remission" [77]
- Acute, symptomatic objectively-diagnosed SVT within 5 days of potential enrollment.
    - Defined as thrombosis involving one or more splanchnic veins (portal, hepatic, splenic, or mesenteric vein) without evidence of portal cavernoma or collateral portosystemic circulation[2] seen as a filling defect on CT, MRI, or doppler ultrasound imaging in part or all of the lumen.[78]
- Willing to sign informed consent.

Exclusion criteria:

- Severe liver disease (e.g., known cirrhosis with a Child-Pugh score of B or C).

- AST or ALT levels > 3 x upper limit of normal (ULN).
- Budd-Chiari syndrome (BCS).
- History of or ongoing variceal bleeding.
- Portal vein cavernoma at the time of diagnosis.
- Anticipated abdominal surgical procedure.
- Established bleeding diathesis.
- Platelet count < 50,000/mm^3.
- Creatinine clearance < 30 mL/min.
- History of heparin-induced thrombocytopenia.
- Low life expectancy (less than 3 months).
- Unable to use parenteral or oral medication.
- Requirement for anticoagulation with vitamin K antagonist (e.g., mechanical valves).
- Pregnancy or lactation.
- Taking medications with drug-drug interaction(s) to or hypersensitivity to DOACs or LMWHs (or other contraindication to either DOACs or LMWHs).
- Prescence of myeloproliferative neoplasm (MPN).
- Non-melanoma skin cancer.

Recruitment

Eligible patients will be recruited from 3 Canadian tertiary care sites in Ottawa, London, and Halifax. Principle investigators of this study have established strong research relationships with investigators at these sites through CanVECTOR and other platforms, experts have a good

track-record of managing patients with SVT and cancer, and these sites receive a considerable number of referrals of this study's patient populations of interest. These will be used to evaluate whether we can recruit over 12 months an adequate volume of patients to inform a larger scale multisite trial. Patients who were potentially eligible will be documented, including their eligibility status and reason(s) for ineligibility, consent discussion or lack of, and randomization.

Randomization, Allocation, and Blinding

After consenting consecutive patients, they will be randomized with a 1:1 ratio to receive either DOAC or LMWH. A web-based computerized randomization sequence using variable permutate block sizes will be utilized to determine allocation for each patient. Participants will be notified of clinical course of their condition and who to contact if needed.

Based on the nature of the interventions (pill vs. injection), blinding of participants and investigators can be challenging. Our study will be a Prospective Randomized Open, Blinded End-point (PROBE) trial. Our clinical outcome assessors, analyzers, adjudication committees, laboratory personnel, and imaging specialists will be blinded to study arm allocations. Allocation will be concealed before randomizing patients via central randomization. In addition, our use of hard, objective clinical endpoints will help to reduce bias. Additionally, missing data and loss to follow-up cases will be carefully considered for any difference across trial arms. Our protocol and statistical analysis plans will also be finalized prior to starting the trial. All other procedures will be kept the same for participants in both study arms to further limit biases of an open-label design.

Data Collection

Data will be collected at baseline and 1, 3, and 6 months after the baseline visit. Imaging will be conducted at the last follow-up visit to assess for recanalization of SVT. Recurrent VTE will include objectively-confirmed recurrent SVT (e.g. clot in a previously patent splanchnic segment)[5], PE (confirmed through CTPA or V/Q scans), and/or DVT (confirmed through Doppler ultrasound or venography) of the lower/upper limbs. Patients will be assessed virtually or in-person at 1, 3, and 6 months after randomization. Patients with suspected DVT/PE will undergo imaging and if confirmed, will be treated with current clinical guidelines, as will any medical emergency that arises. We will also evaluate incidences of clinically-relevant bleeding (including major bleeding and clinically-relevant non-major bleeding (CRNMB)) according to ISTH criteria from patient self-reports and by reviewing the local site's medical records.[13,14] We will assess use of any concomitant medications, cancer progress/history, compliance with anticoagulant allocation, any adverse events (including serious adverse events), patients' diary/notes, quality of life (using the EQ-5D-5L questionnaire), and medical comorbidities. Local sites will be asked to fill in the primary/secondary endpoints and adverse/other outcomes using the trial's electronic case report forms.

Outcomes

Pilot trial: The primary feasibility endpoint will be the mean number of patients recruited per site per month, during 1 year of recruitment.

We will also determine the rates of participant eligibility (proportion of patients who are eligible from those screened for the study), consent (proportion of patients who provide consent

from those who are eligible), retention (proportion of patients who continue the study at follow-ups), study completion (proportion of patients who complete the trial procedures), and adherence (proportion of patients who adhere to the study drug allocated to them through counting pills and electronic blister-packs), as secondary outcomes. Outcomes are defined below.

Clinical outcomes: 1) adjudicated clinically-relevant bleeding at 6 months of randomization into study combining major bleeding[13] and CRNMB[14] according to the ISTH definitions; 2) adjudicated recurrent VTE.

Full-Scale trial: Based on results of our systematic review and survey of expert recommendations, our primary efficacy outcome is rate of clinically-relevant bleeding at 6 months of randomization into study. We will use ISTH's definition of major bleeding[13] and CRNMB[14] to adjudicate the occurrence of the primary outcome. Trained and blinded members of the independent adjudication committee will consistently assess each bleeding case for meeting criteria of the primary outcome. Secondary efficacy and safety outcomes will include the following at 3- and 6-month follow-ups: rate of recurrent VTE, all-cause mortality, SVT extension, vein recanalization, major bleeding, CRNMB, as well as health-related quality of life (using the EQ-5D-5L questionnaire) and the incremental cost-effectiveness ratio (ICER).

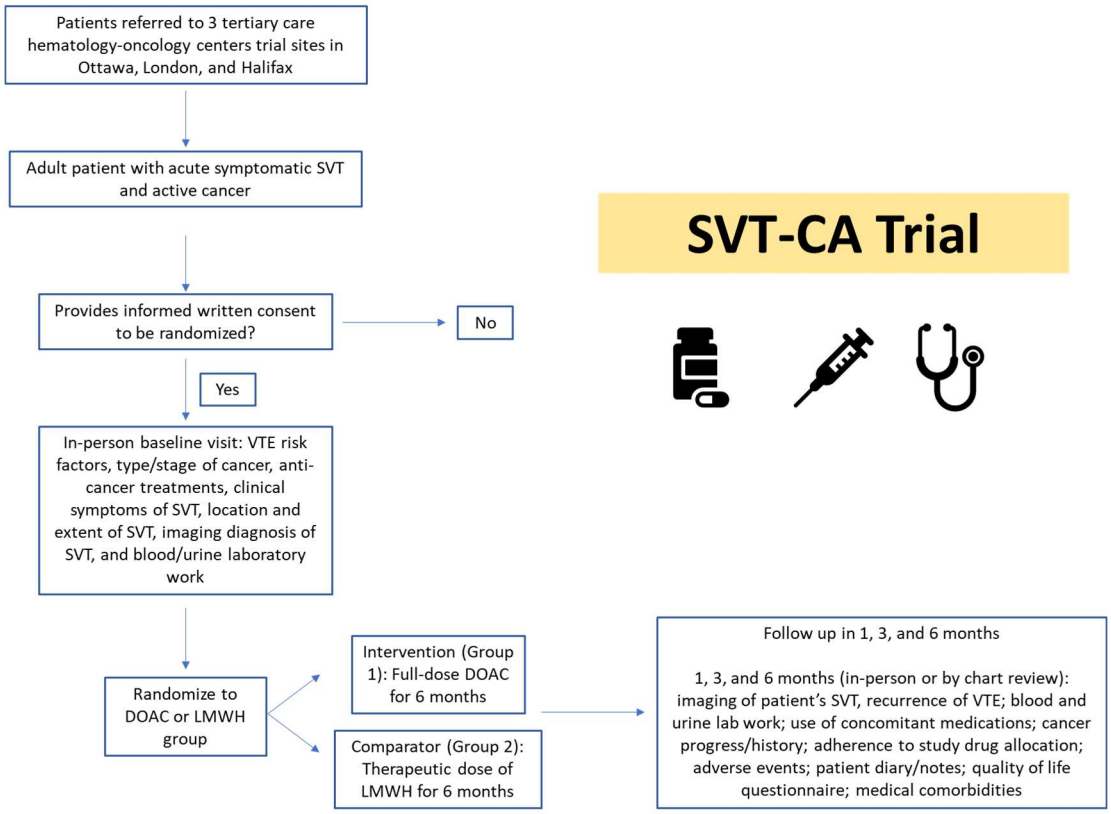

Figure 1. SVT-CA Trial Flow.

Sample Size

Pilot trial: During the recruitment period of 1 year, we plan to recruit 10 patients per month at each site (overall 3 sites). This totals to a minimum of 360 patients. From our past trials, we have found 12 months to be enough time to start and conduct clinical trials for patients with VTE and to get to properly assess the primary/secondary outcomes of pilot trials.[79–81] A low rate of loss to follow-up (e.g. 10%) will be considered as has been used in previous trials assessing management of cancer-associated acute VTE.[82] This rate of recruitment would allow us to reach about 2.75% of the estimated required sample size for a full-scale multisite trial (calculation shown below).

Progression to a full-scale trial: We will use a traffic light system with predefined measurements to evaluate the success of the pilot trial. Progression of each feasibility criteria will be assessed separately and full progression to a full-scale trial will be determined using the worst-performing criterion.[83] CanVECTOR has about 30 actively recruiting sites with many participating in acute DVT clinical trials. For recruitment of the calculated sample size, 20 sites recruiting an average of 10 patients per month would require 66 months.

- Green (no concerns to proceed to full-scale multisite trial): 1) recruiting at least 80% of target participants (8.0 patients per month per site); 2) 90% retention; 3) >70% adherence.
- Yellow (issues to be fixed before proceeding to full-scale multisite trial): 1) recruiting 30-80% of target participants (3.0-8.0 patients per month per site); 2) 70-90% retention; 3) 50-70% adherence.
- Red (likely not feasible): 1) not meeting conditions of either green or yellow lights.

Full-Scale trial: With the use of an estimated incidence of the primary outcome of 3.91% at 6 months with LMWH and a noninferiority margin of 1% for the absolute risk, we calculated that we would need to enroll 5893 patients in each trial arm for the study to have 80% power to show the non-inferiority of DOACs, at a one-sided alpha level of 0.025. This sample was increased to 6548 patients in each trial arm to account for up to 10% of patients' loss to follow-up, for a total of 13,096 patients. Given the number of patients needed in the full-scale trial, it is important to document feasibility of recruitment in a pilot trial before moving to a full-scale trial. A pilot trial is necessary as we also need to evaluate whether our research protocol and recruitment approaches are workable on a smaller-scale first. Another important reason for

the pilot trial is to obtain preliminary data on our proposed primary efficacy outcome to adjust calculation of a sample size if needed.

Sample Size Justification

We base our sample size calculation on the MCID in risk of clinically-relevant bleeding between anticoagulation regimens based on our recent survey of experts.[66,76] Prior to the survey, we conducted a systematic review and found that patients with cancer who received anticoagulation had an incidence rate of 7.81 per 100 patient-years for clinically-relevant bleeding. In a recent Delphi survey we conducted, Canadian experts in SVT management reported that an increase of 1% in risk of clinically-relevant bleeding was a reasonable MCID.[76]

Statistical Analysis

Pilot trial: We will report feasibility outcomes using descriptive statistics, total recruitment stratified by study site as well proportions (%) and 95% confidence intervals of the rates. Analyses will be done at the completion of the pilot trial. If the trial is feasible, participants of the pilot trial will be included in the full-scale trial. We have not planned for any interim analyses at this time. Study feasibility will be assessed without any subgroups. Exploratory subgroup analysis will however be conducted in the full-scale trial and reported descriptively in the pilot trial.

Full-Scale trial: An intention-to-treat approach will be used for comparing the primary and secondary endpoints between patients in the DOAC and LMWH trial arms. Descriptive

statistics will be presented using mean/median and standard deviation/interquartile range for continuous variables and as frequency (%) for categorical variables. The rates of clinically-relevant bleeding will be compared at 6 months between patients of the 2 study arms using an unadjusted t-test and an alpha of 0.05. A per-protocol approach will also be carried out, without including any participant losses to follow-up or protocol deviations/violations. Proportions will be compared using the Fisher's exact test or chi-square test. A sensitivity analysis will be carried out via the Cox regression model (adjusting for age, sex, and type of SVT; death will be treated as a competing event) to calculate hazard ratios of the primary and secondary outcomes. We will also conduct a sensitivity analysis using logistic regression to determine the odds ratio of clinically-relevant bleeding associated with taking DOACs compared to LMWHs, controlling for the aforementioned predictors. Exploratory subgroup analyses include: 1) age; 2) sex (male or female); 3) self-identified gender; 4) type of SVT (provoked or unprovoked); 5) specific anticoagulant (rivaroxaban, apixaban, edoxaban, tinzaparin, dalteparin, or enoxaparin). 6) patient's ethnicity; 7) SVT secondary to transient or chronic nonmalignant risk factors; 8) site of SVT (portal, hepatic, splenic, or mesenteric vein); 9) type of cancer; 10) recanalization of SVT (complete, partial, or none); 11) recurrence of VTE (yes or no).

Ethical Considerations

We will seek for research ethics approval for conducting this study at the Ottawa Hospital Research Institute (OHRI) along with at each local partnering site's research ethics board prior to enrolling patients. Approval will be sought from the Ottawa Health Science Network (OHSN) and Clinical Trials Ontario (CTO) to conduct this trial. Patients will be recruited through obtaining informed consent prior to starting study activities. A Data Safety and Monitoring Board (DSMB)

will be involved to review the safety of the study's data, including a specialist in clinical thrombosis, trialist expert, and biostatistician; these individuals will otherwise not be involved in the study. All adverse outcomes and protocol deviations/violations will be provided to the DSMB for review along with the planned study clinical outcomes. The DSMB will review the safety data and pilot trial's progress after half of the target number of participants have been recruited. They will make recommendations to the steering committee to either stop the pilot trial and/or to adjust the protocol if there are safety issues or it is not feasible to move on to a full-scale trial.

Our study protocol is written in accordance with the SPIRIT 2022 outcomes[84] and follows the principles of Good Clinical Practice and Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2). Clinicians/Researchers conducting this study or collecting data will receive appropriate accesses/permissions, certifications, and trainings.

Trial Management

The trial will be coordinated by OHRI's Clinical Epidemiology Unit and OHRI acting as the study sponsor. This is where the Nominated Principal Applicant (NPA) is located. A multicenter study research coordinator with expertise in VTE clinical trials will be selected. This study coordinator will be supervised by the principal applicants and will oversee the day-to-day operations of the study at the trial sites. Local study coordinators will be responsible for full conduct of the study (e.g. screening, recruitment, etc.) at their respective site. The OHRI Data Management Services group will design, implement, and maintain the web-based randomization system and the data management system with established quality assurance protocols. The study's statisticians will oversee the study's randomization and data management. Our

multidisciplinary study team is composed of researchers and clinicians with expertise in clinical epidemiology and trials, internal medicine, and hematology.

A multidisciplinary steering committee with experts in clinical and methodological components of this trial will be assigned to manage the overall conduct of the study, meeting once every 6 months by videoconferencing to monitor the study progress and discuss issues. The committee will be responsible for the study's design, execution, analysis, and feasibility evaluation using input from the DSMB.

Trial Status

The SVT-CA trial was designed in 2023 after promising results from recent meta-analysis and Delphi expert surveys.[66,76] The trial team is looking to apply for peer-reviewed funding. Trial recruitment will begin once funding is secured. Our steering committee has been established. Recruitment will continue for 12 months after trial initiation. Preliminary results will be made available upon data collection and analysis.

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