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Treatment response and bleeding events associated with anticoagulant therapy of portal vein thrombosis in cirrhotic patients: Systematic review and meta-analysis

Babu P. Mohan[a], Veeraraghavan Meyyur Aravamudan[b], Shahab Rasool Khan[c], Suresh Ponnada[d], Ravishankar Asokkumar[e], Douglas G. Adler[a]

University of Arizona, Banner University Medical Center, Tucson, AZ, USA; Woodlands Health Campus, Singapore; Rush University Medical Center, Chicago, IL, USA; Carilion Roanoke Memorial Hospital, Roanoke, Virginia, USA; Singapore General Hospital, Singapore; University of Utah Health, Salt Lake City, UT, USA

Abstract

Background Well-defined guidelines for the treatment of portal vein thrombosis (PVT) in patients with cirrhosis are lacking, given the paucity of robust data. Among the available treatment options the best choice is unknown.

Methods We conducted a comprehensive search of multiple electronic databases and conference proceedings (through December 2019) to identify studies that reported on the use of anticoagulants in the treatment of PVT in patients with cirrhosis. Our goals were to evaluate the pooled odds ratio (OR) and pooled rate of treatment responders and bleeding events.

Results A total of 17 studies were included: 648 patients were treated with anticoagulation and 96 were controls. Pooled OR for treatment responders was 5.1 (95% confidence interval [CI] 2.5-10.2, P = 0.001) and pooled OR for bleeding was 0.4 (95%CI 0.1-1.5, P = 0.2) for anticoagulation treatment versus control. Pooled rate of treatment responders with anticoagulation was 66.7% (95%CI 58.3-74.1) compared to 26% (95%CI 14.2-42.7) for the control group. Pooled rate of bleeding seemed comparable (7.8%, 95%CI 4.5-13.3, and 15.4%, 95%CI 4.3-42.7). On subgroup analysis, pooled rates of treatment responders and bleeding events seemed similar between low molecular weight heparin, vitamin K antagonists, and direct oral anticoagulants.

Conclusions Our study demonstrated that anticoagulation is effective and safe in the treatment of PVT in patients with cirrhosis. Owing to the comparable outcomes, direct oral anticoagulants may be considered as first-line treatment, depending on patient preferences.

Keywords Portal vein thrombosis, cirrhosis, direct oral anticoagulants, meta-analysis

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[a]Division of Gastroenterology and Hepatology, University of Utah School of Medicine, Salt Lake City, UT, USA; [b]Department of Medicine, Woodlands Health Campus, Singapore; [c]Section of Gastroenterology, Rush University Medical Center, Chicago, Illinois, USA; [d]Internal Medicine, Carilion Roanoke Memorial Hospital, Roanoke, Virginia, USA; [e]Department of Gastroenterology and Hepatology, Singapore General Hospital, Singapore

Conflict of Interest: None

Correspondence to: Douglas G. Adler MD, FACG, AGAF, FASGE, Professor of Medicine, Director of Therapeutic Endoscopy, Directory, GI fellowship Program, Gastroenterology and Hepatology, University of Utah School of Medicine, Huntsman Cancer Center, 30N 1900E 4R118, Salt Lake City, Utah 84132, USA,
e-mail: Douglas.adler@hsc.utah.edu

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Introduction

Portal vein thrombosis (PVT) is defined as a clot within the portal vein trunk and/or its intrahepatic branches, the mesenteric vein, the hepatic veins and the splenic veins. PVT can be completely or partially occlusive and can be a life-threatening event if it extends into the superior mesenteric vein [1,2]. Although the impact of PVT on the natural history of patients with cirrhosis is not well established, some evidence suggests that PVT may contribute to a poor prognosis in patients undergoing liver transplantation [3].

The natural course of untreated PVT is not known. Several studies have shown spontaneous resolution and/or no change in 30-75% of cases, and worsening in most of the remainder [4]. Evidence suggests that a majority of these patients will benefit from some form of anticoagulation.

Robust data on the optimal management of PVT in patients with cirrhosis are lacking and current guidelines do not propose definitive evidence-based treatment strategies [3]. The best choice of anticoagulation is unknown in cirrhotic patients with PVT.

The classes of anticoagulant therapy for PVT in cirrhosis are vitamin K antagonists (VKA), low molecular weight heparin (LMWH), and, to a lesser extent, direct oral anticoagulants (DOAC). DOAC in this context have been used in an "off-label" manner and current evidence is limited on its use in the treatment of PVT in patients with cirrhosis. We conducted this meta-analysis to update our knowledge of the use of anticoagulation in PVT patients with cirrhosis, focusing particularly on evidence concerning the use of DOAC.

Materials and methods

Search strategy

We conducted a comprehensive search of several databases and conference proceedings, including PubMed, EMBASE, Google-Scholar, LILACS and Web of Science databases (earliest inception to December 2019). We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [5,6], by using a predefined protocol to identify studies reporting on the treatment of PVT in patients with cirrhosis. PRISMA and MOOSE checklists are provided in Appendices 2 and 3 respectively.

An experienced medical librarian helped with the literature search, using inputs from the study authors. The detailed search strategy is provided in Appendix1. Three authors (BPM, VM, SRK) independently reviewed the title and abstract of studies identified in the primary search and excluded studies that did not address the research question, based on pre-specified exclusion and inclusion criteria. The full text of the remaining articles was reviewed to determine whether it contained relevant information. Any discrepancy in article selection was resolved by consensus and in discussion with a co-author.

The bibliographic section of the selected articles, as well as the systematic and narrative articles on the topic were manually searched for additional relevant articles.

Study selection

In this meta-analysis, we included studies that evaluated the performance of anticoagulants in the treatment of PVT in patients with cirrhosis. Studies were included irrespectively of the site of thrombus (main portal vein and/or branches, main mesenteric vein and/or branches, main hepatic vein and/or branches, and main splenic vein and/or branches), inpatient/outpatient setting, geography, and abstract/manuscript status, as long as they provided data needed for the analysis. Special attention was focused on data pertaining to patency of the portal vein and its branches, the mesenteric vein, splenic veins, and hepatic veins.

Patients treated with VKA were pre-treated with LMWH for 5-7 days and/or until the international normalized ratio (INR) increased at least to 2.0. The dose of VKA was adjusted to a target INR of 2.0-3.0. LMWH was administered at a treatment dose of 1 mg/kg body weight subcutaneously. Danaparoid sodium (Orgaran; MSD, Tokyo, Japan) was administered as intravenous drip infusion at a dose of 2500 units/day for a total of 2 weeks.

Response to treatment was assessed by the change in diameter of the thrombus at scheduled follow up. Complete resolution was defined as disappearance of all evidence of thrombosis, determined by transverse computed tomography (CT). Partial resolution was defined as at least a 30% reduction in the long diameter of the main thrombus and/or 50% reduction in the cross-sectional area, without evidence of appearance of new thrombi. Patients with partial or complete resolution were considered as responders to treatment.

Clinically significant bleeding was defined based on the location of critical organs—cranium, spine, ocular, retroperitoneal, pericardial, urinary tract, and intramuscular with compartment syndrome—along with a decrease in hemoglobin level ≥2 g/dL and the need for transfusion of blood products.

Our study's exclusion criteria included: 1) studies with underlying hepatocellular carcinoma and/or metastases; 2) studies with other malignancy-related PVT; 3) studies reporting on arterial thrombosis; 4) studies reporting on patients with underlying thrombogenic hematologic disorders unrelated to cirrhosis; 5) studies on patients with Budd-Chiari syndrome; 6) studies reporting on patients with prior trans-jugular intra-hepatic portosystemic shunt procedure; 7) studies with a sample size <10 patients; 8) studies in a pediatric population (age <18 years); and 9) studies published in a language other than English.

In case of multiple publications from the same cohort or overlapping cohorts, data from the most recent and/or most appropriate comprehensive report were included. PVT was diagnosed by helical CT and/or Doppler ultrasonography. Angiography and/or magnetic resonance imaging was used as and when needed to confirm a doubtful diagnosis.

Data abstraction and quality assessment

Data on study-related outcomes in the individual studies were abstracted onto a standardized form by at least 2 authors (VM, SRK), and 2 authors (BPM, SRK) did the quality scoring independently. Data from randomized trials and case-control studies were calculated as number of reported events (n) out of total number of patients (N) from each study. Since the collected data were treated in similar fashion to those from

single-group cohort studies, we used the Newcastle-Ottawa scale to assess the quality of studies [7]. The details are given in Supplementary Table 1.

Outcomes assessed

Pooled rate of treatment responders, anticoagulation versus control, and pooled rate of bleeding, anticoagulation versus control. Subgroup analysis was based on the type of anticoagulant (VKA, LMWH or DOAC).

Statistical analysis

We used meta-analysis techniques to calculate the pooled estimates in each case, following the random-effects model. When the incidence of an outcome was zero in a study, a continuity correction of 0.5 was added to the number of incident cases before statistical analysis [8]. We assessed heterogeneity between study-specific estimates using the Cochran Q statistical test for heterogeneity [9,10] and the I^2 statistic [11,12]. In this test, values of <30%, 30-60%, 61-75% and >75% were suggestive of low, moderate, substantial and considerable heterogeneity, respectively [13]. Publication bias was ascertained qualitatively, by visual inspection of a funnel plot, and quantitatively, by the Egger test [14]. When publication bias was present, further statistics using the fail-safe N test and Duval and Tweedie's "Trim and Fill" test was used to ascertain the impact of the bias [15]. Three levels of impact were reported, based on the concordance between the reported results and the actual estimate if there were no bias. The impact was reported as minimal if both versions were estimated to be the same, modest if effect size changed substantially but the final finding would still remain the same, and severe if the basic final conclusion of the analysis was threatened by the bias [16]. We ran meta-regression analysis based on the random-effects Knapp-Hartung method to evaluate effects of variables on the analyzed outcomes. All analyses were performed using Comprehensive Meta-Analysis (CMA) software, version 3 (BioStat, Englewood, NJ).

Results

Search results and population characteristics

From an initial total of 1147 studies, 523 records were screened and 71 full-length articles were assessed. 17 studies were included in the final analysis [17-33]. Five studies reported on LMWH [17,22,23,25,32], 8 reported on VKA [19-21,24,26,27,29,33], and 3 reported on DOAC [26,29,31]. Two studies reported anticoagulation in general [18,30], and one study used danaparoid alone [28]. Six studies reported on patients with PVT who were not treated with anticoagulation and were used as the control cohort [20,21,23,25,30,32]. The schematic diagram of the study selection is illustrated in Supplementary Fig. 1.

Baseline population characteristics were comparable between the VKA, LMWH, DOAC, and control groups. The mean and/or median age ranged from 41-71 years, with a predominantly male population (70.6%). Alcoholic (45.3%) and viral (40.3%) causes of cirrhosis were the most common, followed by autoimmune and biliary causes (14.4%). There were 144 patients with Child-Pugh A, 182 patients with Child-Pugh B, and 121 with Child-Pugh C cirrhosis. The majority of the studies had patients screened for esophageal varices before the initiation of anticoagulation. Patients with grade II or III esophageal varices were banded and anticoagulation initiation was delayed until 15 days after the last banding session. Unfortunately, studies did not report uniformly on the details of banding prior to anticoagulation initiation. The basic study and population characteristics are described in Supplementary Table 1.

Characteristics and quality of included studies

Two studies were prospective and the rest were retrospective in nature [23,32]. Two were multicenter studies [22,26] and the rest were single-centered. None were population-based. The details of the quality assessment are summarized in Supplementary Table 2. Overall, 8 studies were considered to be of high quality [20-24,26,29,32] and the rest were of medium quality. There were no low quality studies.

Outcomes

A total of 744 patients were included in the analysis from the 17 studies [17-33]. A pooled odds ratio (OR) was calculated from 6 studies that compared anticoagulation to controls. The pooled OR for treatment responders was 5.1 (95% confidence interval [CI] 2.5-10.2, P=0.001, I^2=13%) (Fig. 1), and the pooled OR for bleeding was 0.4 (95%CI 0.1-1.5, P=0.2, I^2=0%) (Fig. 2).

The pooled rate of treatment responders was 66.7% (95%CI 58.3-74.1, I^2=72.7%) and the pooled rate of treatment responders in the control group (no treatment), was 26% (95%CI 14.2-42.7, I^2=36.7%) (Supplementary Fig. 2). The pooled rate of bleeding with anticoagulation was 7.8% (95%CI 4.5-13.3, I^2=66.2%), and the pooled rate of bleeding in the control group was 15.4% (95%CI 4.3-42.7, I^2=0%) (Supplementary Fig. 3).

Subgroup analysis

Subgroup analysis was based on the anticoagulation type, i.e., LMWH, VKA, and DOAC: 155 patients were treated with LMWH, 315 with VKA, and 70 with DOAC. The pooled rate of treatment response was 60.7% (95%CI 41.5-77.2) for LMWH, 66% (95%CI 51.1-78.3) for VKA, and 76.7% (95%CI 45.3-92.9)

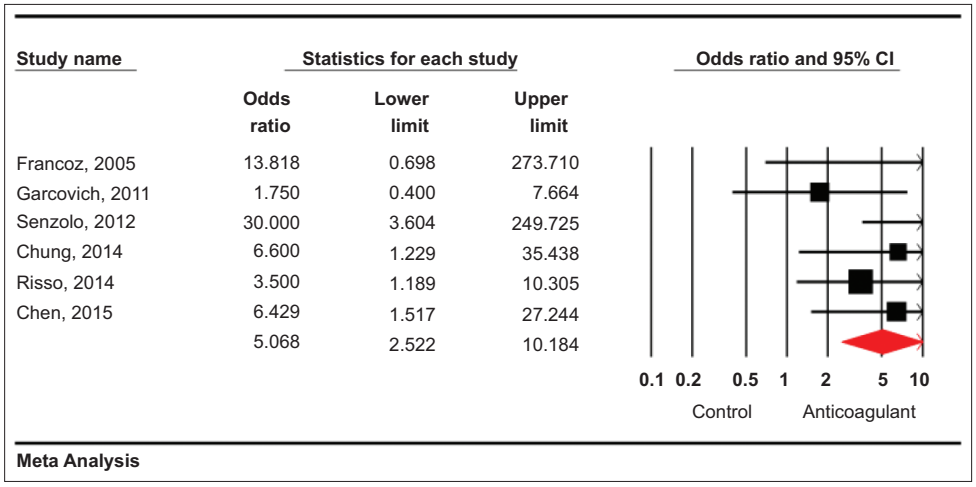

Figure 1 Forest plot. Treatment responders: Pooled odds ratio (OR), anticoagulation vs. control

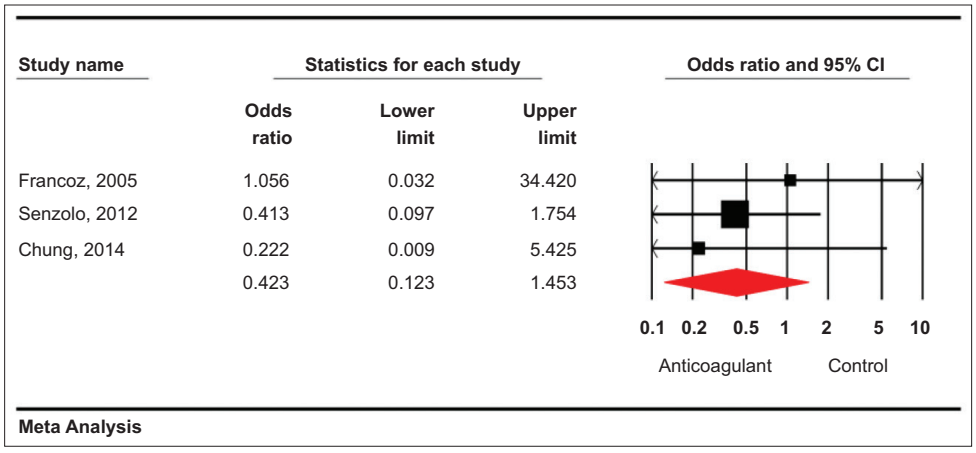

Figure 2 Forest plot. Bleeding: Pooled odds ratio (OR), anticoagulation vs. control

for DOAC (Supplementary Fig. 4). The pooled rate of bleeding was 7.2% (95%CI 2.1-21.6) for LMWH, 9.3% (95%CI 3.9-20.6) for VKA, and 7.9% (95%CI 1.7-29.9) for DOAC (Supplementary Fig. 5). These rates appeared comparable (Table 1).

Meta-regression analysis based on Child-Pugh classification

Child-Pugh classifications A, B and C did not significantly affect the pooled rates of treatment success or the pooled rates of bleeding. The calculated 2-sided P-value of the intercept was 0.39: Child A was 0.15, Child B was 0.11, and Child C was 0.15.

Validation of meta-analysis results

Sensitivity analysis

To assess whether any one study had a dominant effect on the meta-analysis, we excluded one study at a time and analyzed its effect on the main summary estimate. On this analysis, no single study significantly affected the outcome or the heterogeneity.

Heterogeneity

We assessed the dispersion of the calculated rates using the I^2 percentage values. The pooled OR with treatment responders and/or bleeding demonstrated minimal to no heterogeneity. The pooled rate of treatment responders with anticoagulation demonstrated considerable to moderate heterogeneity. Meta-regression analysis and subgroup analysis did not demonstrate a statistical explanation for the observed heterogeneity.

Publication bias

Based on visual inspection of the funnel plot, as well as quantitative measurement that used the Egger regression test, there was evidence of publication bias. Further statistics

Table 1 Summary of pooled results

Group	Treatment responders				Bleeding			
	Pooled rate	95%CI	I^2 %	P-value	Pooled rate	95%CI	I^2 %	P-value
All anticoagulants vs. controls	OR 5.1	2.5-10.2	13	0.001	OR 0.4	0.1-1.5	0	0.2
All anticoagulants	66.7%	58.3-74.1	72.7	0.001	7.8%	4.5-13.3	66.2	0.33
Control	26%	14.2-42.7	36.7		15.4%	4.3-42.7	0	
VKAs	66%	51.1-78.3	80.7		9.3%	3.9-20.6	78.2	
LMWH	60.7%	41.5-77.2	57		7.2%	2.1-21.6	0	
DOAC	76.7%	45.3-92.9	88.5		7.9%	1.7-29.9	30.3	
LMWH vs. VKAs				0.63				0.33
DOACs vs. LMWH				0.35				0.74
DOAC vs. VKA				0.5				0.9

CI, confidence interval; OR, odds ratio; VKA, Vitamin-K antagonists; LMWH, low molecular weight heparin; DOAC, direct oral anticoagulation

using the fail-safe N test and Duval and Tweedie's "Trim and Fill" test revealed that the impact of the possible publication bias appeared to be minimal and would not change the calculated estimate or the conclusion of this meta-analysis (Supplementary Fig. 6).

Discussion

This study demonstrated that the pooled OR of treatment response was statistically significant (OR 5.1, 95%CI 2.5-10.2; P = 0.001) with respect to anticoagulation therapy of PVT, as compared to controls, in patients with cirrhosis. The pooled OR of bleeding events was 0.4 (95%CI 0.1-1.5) and was not significant (P = 0.2). To the best of our knowledge, this study is the largest and most current review of anticoagulation therapy of PVT in patients with cirrhosis.

Our study results add important data to the current literature, since this is the first study to analyze the pooled rates of DOAC in the treatment of PVT, and the first to analyze the effect of Child-Pugh classification on the pooled rates by meta-regression methods. However, it is important to note that meta-regression analysis is a weak statistical tool in the assessment of a variable's predictive effects on the pooled outcomes, and the result is not in accordance with current clinical experience. Anticoagulation is completely different in a well-compensated cirrhotic patient compared to a decompensated patient. Studies included in this analysis did not specify the treatment in relation to the Child score.

The pooled rate of treatment response with anticoagulation was 66.7% and the pooled rate in the control group was 26%. Based on the subgroup analysis, the pooled rate of treatment response was 60.7% for LMWH, 66% for VKA, and 76.7% for DOAC. Although our results do not establish causality, they clearly indicate that anticoagulation therapy of PVT in patients with cirrhosis is more beneficial than no treatment. The treatment duration in the studies included ranged from 2 weeks in the case of danaparoid followed by VKA to 17 months in the case of LMWH. In the case of DOAC the treatment was given for 6 months.

Patients with cirrhosis are considered to be more prone to develop PVT compared to patients without cirrhosis, with a reported incidence in the range of 9-11%, far higher than that of the general population [34,35]. Patients with advanced liver cirrhosis and PVT tend to have lower activated partial thromboplastin time and INR. Apart from deranged coagulation parameters, a decreased velocity of portal vein flow, with or without flow reversal, seems to be an important factor predisposing to thrombus formation [36,37]. Based on our results, anticoagulation therapy seems warranted in patients with cirrhosis; however, this cannot be generalized at present, as there are many different phenotypes of cirrhotics and the current major societies differ in their opinion.

The pooled rate of bleeding with anticoagulation was 7.8%: 7.2% with LMWH, 9.3% with VKA, and 7.9% with DOAC. Our analysis demonstrated comparable rates of life-threatening bleeding events with LMWH, VKA, and DOAC. The majority of reported bleeding events, especially variceal, were located in the gastrointestinal tract. Patients with high-grade varices were typically banded before anticoagulation therapy and treatment was typically delayed by 15 days. Variceal bleed with any anticoagulation, especially a DOAC, can be potentially life-threatening. The pooled rate of bleeding in the control group was 15.4%.

Although, the United States Food and Drug Administration has approved novel antidotes for DOAC, they are not widely available for use, especially in resource-limited settings, because of cost issues. LMWH and/or VKA may be a safer option in patients with severe varices, given the readily available antidotes. In the studies analyzed, no bleeding-related deaths were reported. Based on our meta-

regression analysis, Child-Pugh classification for the severity of cirrhosis did not seem to influence the measured outcomes. Currently, DOAC are not recommended for use in Child-Pugh C cirrhosis.

Overall, the strengths of this review are the systematic literature search with well-defined inclusion criteria, the careful exclusion of redundant studies, the inclusion of good quality studies with detailed extraction of data, the rigorous evaluation of study quality, and the statistics to establish or refute the validity of the results of our meta-analysis. Analysis of DOAC and meta-regression covariate analysis based on the Child-Pugh classification are new additions to the current literature.

There were limitations to this study, most of which are inherent to any meta-analysis. Our analysis included studies retrospective in nature, contributing to selection bias. Although the treatment response was high, we were not able to specify the magnitude of the treatment in relation to the anatomical location of the response, and there was no information on portal cavernoma. Heterogeneity was noted in the analysis of treatment responders, especially in the treatment with VKA. Variability in the time to achieve a target INR with VKA is a plausible explanation, along with the variability in treatment dosage, duration of heparin bridging and differences in anticoagulation medication. We were not able to analyze the treatment outcomes based on the model for end-stage liver disease score, because of the paucity of data. We were not able to evaluate the role of β-blockers on primary prevention with PVT and plan for anticoagulation.

Our results are comparable with previously conducted meta-analyses [38,39], which reported a recanalization rate of 66-71% with anticoagulation treatment for PVT in patients with cirrhosis with no excess of major or minor bleedings. In the study sample of Scheiner *et al* [31], 70% of the patients had non-cirrhotic PVT. Nagaoki *et al* [29] used a combination of 3 drugs (danaparoid, ATIII infusion followed by VKA). Hanafy *et al* [26] compared VKA to DOAC in a cohort of patients that consisted entirely of acute PVT from splenectomy in well-compensated HCV cirrhosis. However, based on our sensitivity analysis, we demonstrated that including or removing one study at a time did not affect the pooled outcomes, so this study is still the best available evidence in the literature thus far. Well-conducted randomized studies are warranted to better predict the usefulness of LMWH, VKA, and DOAC in such patients.

In conclusion, our meta-analysis demonstrated that anticoagulation therapy of PVT should be considered in patients with cirrhosis. The risk of major life-threatening bleeding does not seem to be increased in cirrhotic patients with PVT treated with anticoagulants, compared to patients with no treatment. LMWH, VKA, and DOAC are comparable in the resolution of PVT, with a similar risk of life-threatening bleeding events. Therefore, DOACs may be used for the treatment of PVT in patients with cirrhosis, based on patient preferences and characteristics.

Summary Box

What is already known:

- Portal vein thrombosis (PVT) is commonly encountered in patients with cirrhosis and can be life-threatening
- According to the Baveno VI consensus, treatment should be considered in potential liver-transplantation candidates; however, no consensus exists for non-transplant candidates
- The consensus is based on weak data and the main concern is the risk of inducing or aggravating a life-threatening bleeding episode
- Additionally, data on the use of direct oral anticoagulants (DOACs) in PVT are limited

What the new findings are:

- In this meta-analysis of 17 studies, the pooled odds ratio (OR) of treatment responders with any form of anticoagulation therapy for PVT in cirrhotic patients was statistically significant (OR 5.1, 95% confidence interval [CI] 2.5-10.2; P=0.001), when compared to no anticoagulation
- The pooled proportion of treatment responders was 60.7% for low molecular weight heparin (LMWH), 66% for vitamin K antagonists (VKA), and 76.7% for DOACs
- The pooled odds ratio (OR 0.4, 95%CI 0.1-1.5; P=0.2) showed that the bleeding risk in cirrhotic patients receiving any form of anticoagulation therapy for PVT was comparable to that in patients who received no anticoagulation
- The pooled bleeding risk seemed comparable for LMWH, VKAs and DOACs (7.2%, 9.3% and 7.9%, respectively)

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Supplementary Table 1 Study and patient characteristics

Study	Design	Age	Sex (m/f)	Intervention	Total N	Responders	Failures	Bleeding	Bleeding details	Child-Pugh (A/B/C)	F/U Time	Rx duration
Francoz, 2005 [23]	Prospective, single center, Jan 1996 to Dec 2001	48.7	13/6	LMWH	19	8	11	1	1 Post procedural	2/13/4	36 m	8.1 m
		52	7/3	Control	10	0	10	0	NA	2/6/2	NR	NA
Garcovich, 2011 [25]	Retrospective, cross-sectional	NR	NR	LMWH	15	7	6/10	NR	NR	NR	6 m	3-6 m
		NR	NR	Control	15	5	NR	NR	NR	NR	NR	NA
Senzolo, 2012 [32]	Prospective, single center, Jan 2007 to Jan 2008	55.5	25/10	LMWH	35	21	12	4	1 Cerebral, 1 epistaxis, 1 hematuria, 1 variceal	11/16/8	22.53±8.5	6
		52.3	13/8	Control	21	1	15	5	5 Variceal	5/9/7	24.5±8.2	NA
Chung JW, 2014 [21]	Retrospective, Apr 2003 to Jun 2014, single center	59.4	10/4	VKA (Warfarin)	14	11	4	0	NR	6/8/0	4 m	112±62 days
		58.7	NR	Control	14	5	12	2	1 Variceal, 1 subarachnoid	NR	NR	NA
Risso, 2014 [30]	Retrospective	NR	NR	Anticoagulation	50	35	NR	0	All minor	NR	NR	NR
		NR	NR	Control	20	8	NR	NR	NR	NR	NR	NR
Chen, 2015 [20]	Retrospective, Cross-sectional	44.9	NR	VKA (Warfarin)	22	15	7	4	4 Hematemesis/melena, 1 epistaxis, 3 gingival	NR	33	7.6
		47.8	NR	Control	16	4	12	NR	None reported	NR	NR	NR
Naeshiro N, 2015 [28]	Retrospective, Dec 2011 to Apr 2013, single center, Japan	71 (23-83)	13/13	Danaparoid	26	20	6	0	NA	13/8/5	NR	2 weeks
Bento L, 2011 [19]	Retrospective, 2004 to 2009	53 (35-77)	19/9	LMWH/ Acenocoumarol	28	18	10	0	NA	NR	NR	NR
Werner, 2013 [33]	Retrospective, single center, Jan 2005 to Nov 2011	57	44/25	VKA (Warfarin)	69	23	5	0	1 Vaginal bleeding	NR	NR	12 m
Delgado, 2012 [22]	Multicenter, Jun 2003 to Sep 2010	57±12	44/11	LMWH	47	33	22	5	3 GI, 1 post-surgical, 1 dental	NR	19 m	6.8 m
La Mura V, 2018 [27]	Retrospective, 2003 to 2015	59.6±10.7	59/4	VKA (Warfarin)	63	44	19	8	5 Upper GI, 1 intracranial, 1 traumatic, 1 hematuria	0/13/50	NR	NR
Fujiyama S, 2017 [24]	July 2007 and September 2016.	68 (37–84)	47/43	Danaparoid followed by VKA (warfarin)	90	74	16	0	NA	NR	3 years	2 weeks
Amitrano L, 2010 [17]	Jun 2005 to Dec 2006	NR	NR	LMWH	39	30	9	0	NA	NR	NR	7 to 17 m

(*Contd...*)

Supplementary Table 1 (*Continued*)

Study	Design	Age	Sex (m/f)	Intervention	Total N	Responders	Failures	Bleeding	Bleeding details	Child-Pugh (A/B/C)	F/U Time	Rx duration
Scheiner B, 2018 [31]	Retrospective	50±18	2/8	DOAC	10	2	8	1	Portal hypertensive gastropathy	NR	9.2	NR
Hanafy AS, 2018 [26]	RCT, May 2014 to Aug 2017, multicenter, Egypt	46±5	32/8	(DOAC) Rivaroxaban	40	40	0	0	NA	NR	1 year	6.7±1.2
		41.3±2.3	35/5	VKA (Warfarin)	40	18	0	17	All variceal	NR		
Nagaoki, 2018 [29]	Retrospective, Dec 2011 to Apr 2016, single center, Japan	67 (24-83)	17/13	VKA (Warfarin)	30	9	21	2	Rectal varices, angiodysplasia, colon polyp	7/16/7	6 m	6 m
		69 (53-74)	17/3	(DOAC) Edoxaban	20	18	2	3	NR	15/5/0	6 m	6 m
Artaza T, 2018 [18]	Mar 2009 to Sep 2015	NR	NR	anticoagulation	32	23	0	3	NR	NR	NR	7 m

LMWH, low molecular weight heparin; VKA, vitamin K antagonists; DOAC, direct oral anti-coagulants; GI, gastrointestinal; m, months; f/u, follow up; NR, not reported; NA, not applicable

Supplementary Table 2 Study quality assessment

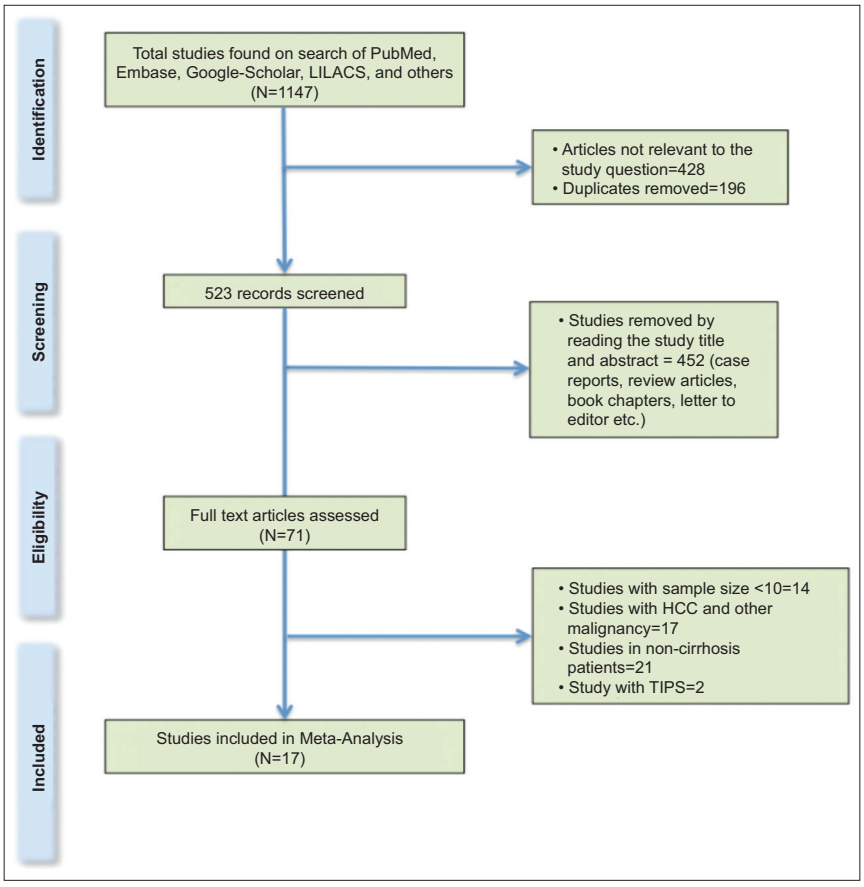
Study	Selection				Comparability	Outcome			Score	Quality
	Representativeness of the average adult in community	Cohort size	Information on clinical outcomes	Outcome not present at start	Factors comparable between the groups	Adequate clinical assessment	Follow up time	Adequacy of follow up	MAX=8	HIGH >6, MEDIUM 4 to 6, LOW <4
	Population based:1; multi-center: 0.5;single-center: 0	>40 patients: 1; 39 to 20: 0.5; <20: 0	Information with clarity: 1; information derived from percentage value: 0.5; unclear: 0	Not present: 1; present: 0	Yes: 1; no: 0	Yes: 1; no: 0	Yes: 1; not mentioned: 0	All patients followed up: 1; >50% followed up: 0.5; <50% followed up OR not mentioned: 0		
Francoz, 2005 [23]	0	0.5	1	1	1	1	1	1	6.5	HIGH
Garcovich, 2011 [25]	0	0.5	1	1	1	1	1	0.5	6	MEDIUM
Senzolo, 2012 [32]	0	1	1	1	1	1	1	1	7	HIGH

(*Contd...*)

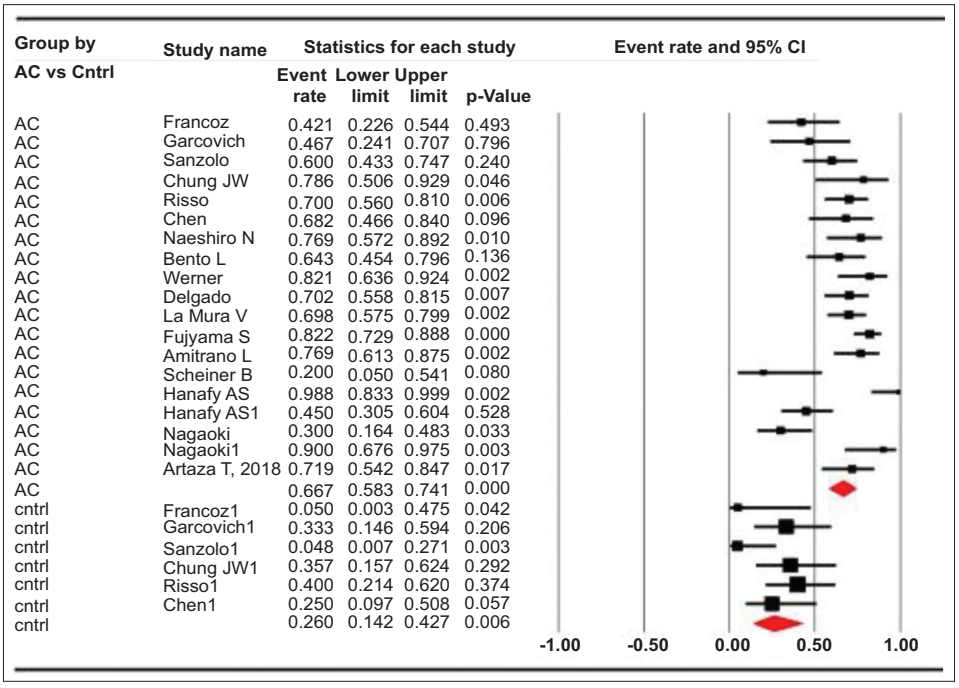
Supplementary Table 2 (*Continued*)

Study	Selection				Comparability	Outcome			Score	Quality
	Representativeness of the average adult in community	Cohort size	Information on clinical outcomes	Outcome not present at start	Factors comparable between the groups	Adequate clinical assessment	Follow up time	Adequacy of follow up	MAX=8	HIGH >6, MEDIUM 4 to 6, LOW <4
	Population based:1; multi-center: 0.5;single-center: 0	>40 patients: 1; 39 to 20: 0.5; <20: 0	Information with clarity: 1; information derived from percentage value: 0.5; unclear: 0	Not present: 1; present: 0	Yes: 1; no: 0	Yes: 1; no: 0	Yes: 1; not mentioned: 0	All patients followed up: 1; >50% followed up: 0.5; <50% followed up OR not mentioned: 0		
Chung JW, 2014 [21]	0	0.5	1	1	1	1	1	1	6.5	HIGH
Risso, 2014 [30]	0	1	1	1	1	1	0	1	6	MEDIUM
Chen, 2015 [20]	0	1	1	1	1	1	1	1	7	HIGH
Naeshiro N, 2015 [28]	0	0.5	1	1	1	1	0	1	5.5	MEDIUM
Bento L, 2011 [19]	0	0.5	1	1	1	1	0	1	5.5	MEDIUM
Werner, 2013 [33]	0	0.5	1	1	1	1	0	1	5.5	MEDIUM
Delgado, 2012 [22]	0.5	1	1	1	1	1	1	1	7.5	HIGH
La Mura V, 2018 [27]	0	1	1	1	1	1	0	1	6	MEDIUM
Fujiyama S, 2017 [24]	0	1	1	1	1	1	1	1	7	HIGH
Amitrano L, 2010 [17]	0	0.5	1	1	1	1	0	1	5.5	MEDIUM
Scheiner B, 2018 [31]	0	0	0.5	1	1	1	1	1	5.5	MEDIUM
Hanafy AS, 2018 [26]	0.5	1	1	1	1	1	1	1	7.5	HIGH
Nagaoki, 2018 [29]	0	1	1	1	1	1	1	1	7	HIGH
Artaza T, 2018 [18]	0	0.5	1	1	1	1	0	1	5.5	MEDIUM

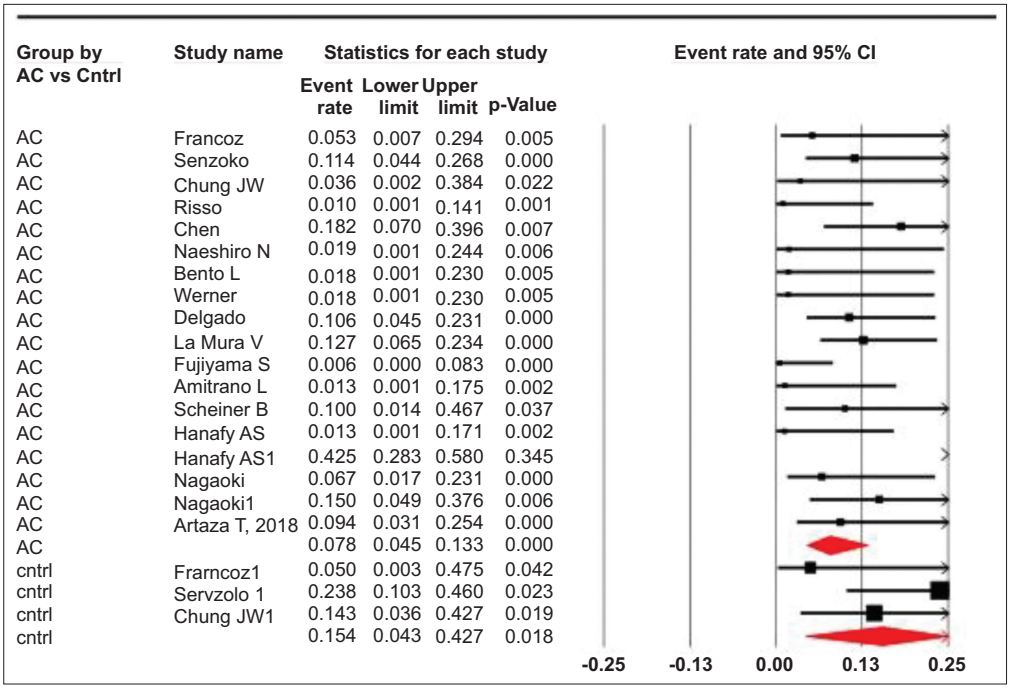
Supplementary Figures



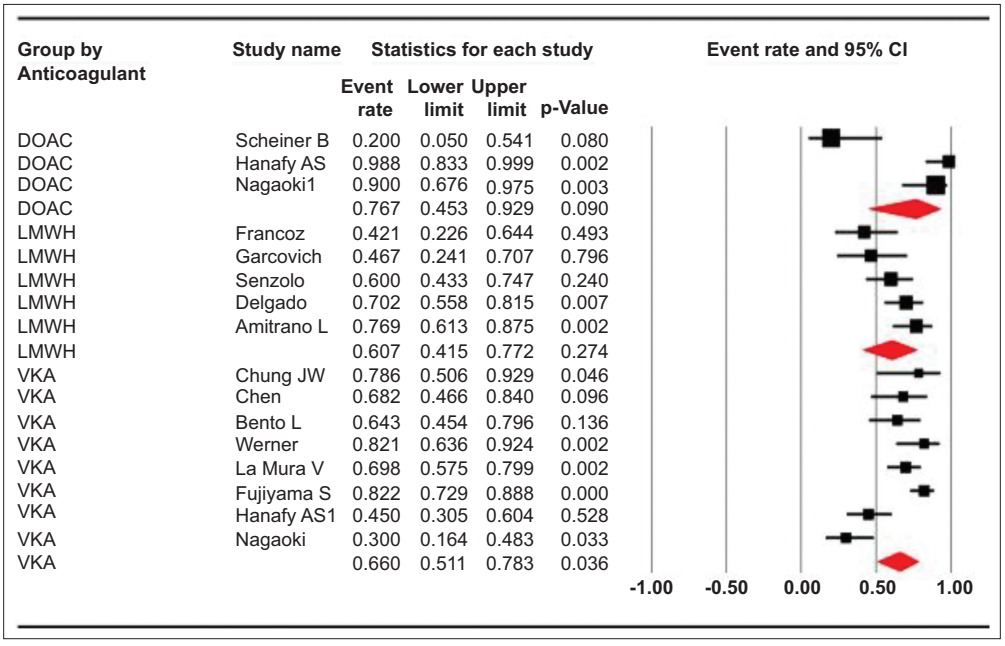
Supplementary Figure 1 Flow diagram of study selection
PVT, portal vein thrombosis; HCC, hepato-cellular carcinoma; TIPS, trans-jugular intra-hepatic porto-systemic shunt



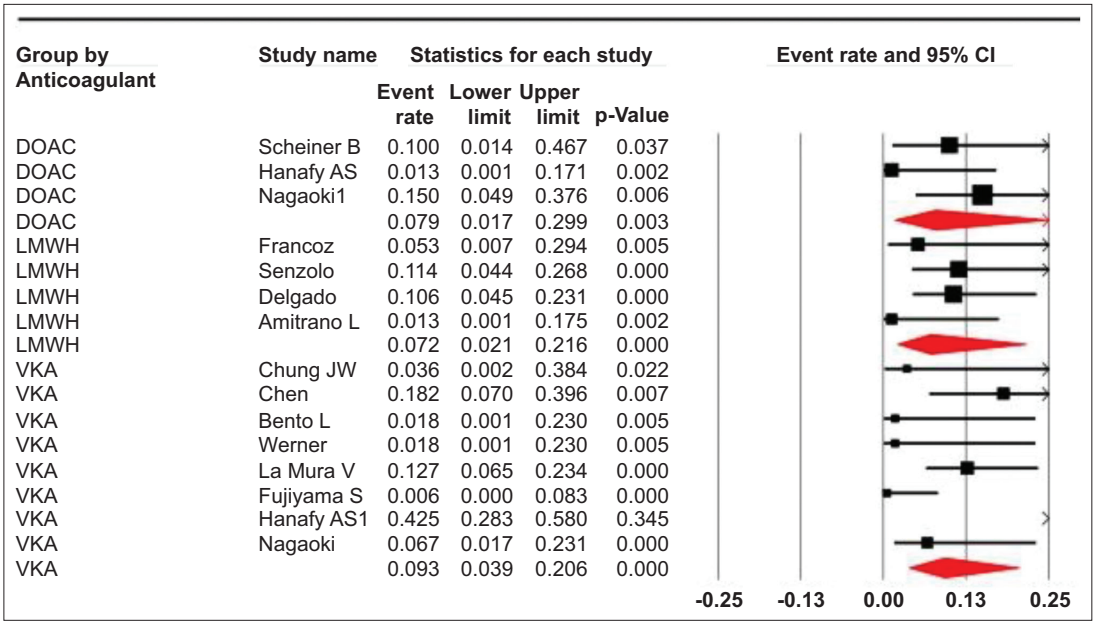
Supplementary Figure 2 Forest plot. Pooled rates, treatment responders: anticoagulation (AC) vs. control (cntrl)



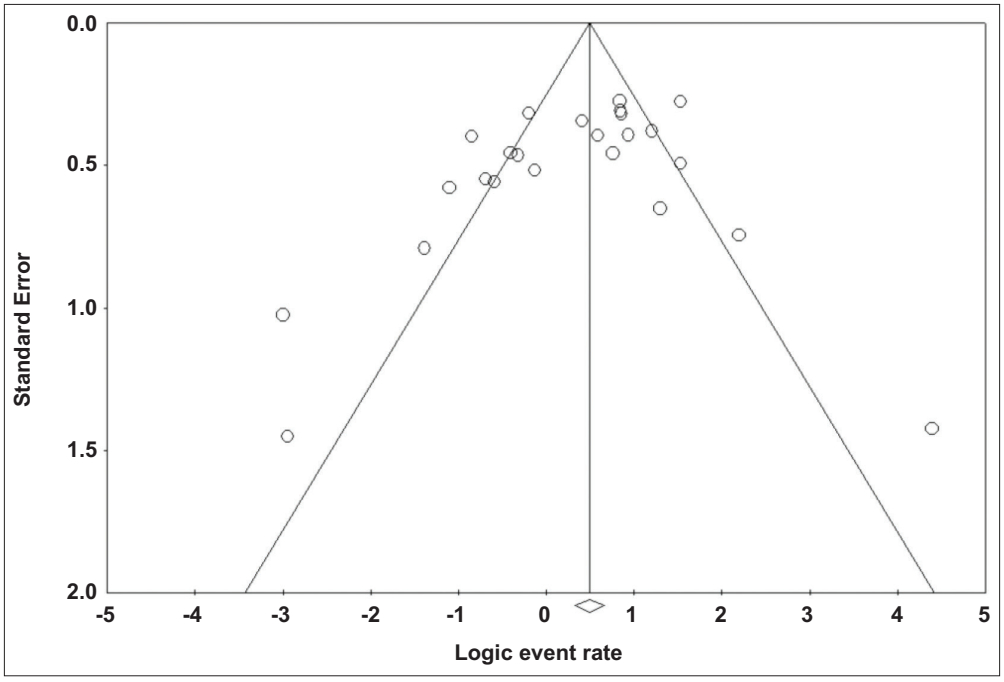
Supplementary Figure 3 Forest plot. Pooled rates, bleeding: anticoagulation (AC) vs. control (cntrl)



Supplementary Figure 4 Forest plot. Subgroup analysis, pooled rates, treatment responders: LMWH vs. VKA vs. DOAC
LMWH, low molecular weight heparin; VKA, vitamin K antagonists; DOAC, direct oral anticoagulants



Supplementary Figure 5 Forest plot. Subgroup analysis, pooled rates, bleeding: LMWH vs. VKA vs. DOAC
LMWH, low molecular weight heparin; VKA, vitamin K antagonists; DOAC, direct oral anticoagulants



Supplementary Figure 6 Publication bias. Funnel plot

Appendix

Appendix 1 Literature search strategy

Database(s): Embase 1988 to 2019, Ovid MEDLINE(R) 1946 to Present and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) Daily, EBM Reviews - Cochrane Central Register of Controlled Trials Dec 2019, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to December 10, 2019

#	Searches	Results
1	exp anticoagulants/	782992
2	anticoagulant therapy/	50181
3	exp 4-Hydroxycoumarins/	25566
4	(anticoagula* or warfarin or heparin or coumadin or acenocoumarol or dicoumarol or phenprocoumon or "ethyl biscoumacetate").ti,ab,hw,kw.	559609
5	or/1-4	924639
6	exp portal vein/ or exp hepatic portal vein/	24430
7	exp thrombosis/ or thrombo*.ti.	593811
8	6 and 7	4640
9	exp portal vein thrombosis/	10220
10	(port* adj1 vein* adj1 thrombo*).ti,ab,hw,kw.	15156
11	or/8-10	17805
12	exp liver cirrhosis/	218036
13	(cirrhotic or cirrhosis).ti,ab,hw,kw.	295561
14	12 or 13	295561
15	5 and 11 and 14	1471
16	limit 15 to english language [Limit not valid in CDSR; records were retained]	1358
17	16 not ((case* adj3 (report* or series or stud*)).ti,ab,hw,kw. or case report/ or exp case study/)	1041
18	17 not ((exp animals/ or exp nonhuman/) not exp humans/)	1032
19	remove duplicates from 18	794

SCOPUS

1	TITLE-ABS-KEY ((anticoagula* OR warfarin OR heparin OR coumadin OR acenocoumarol OR dicoumarol OR phenprocoumon OR "ethyl biscoumacetate"))
2	TITLE-ABS-KEY ((port* W/1 vein* W/1 thrombo*))
3	TITLE-ABS-KEY ((cirrhotic OR cirrhosis))
4	#1 and #2 and #3
5	INDEX(embase) OR INDEX(medline) OR PMID(0* OR 1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)
6	#4 and not #5
7	DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh) OR DOCTYPE(ch)
8	#6 and not #7
9	LANGUAGE(english)
10	#8 and #9

Appendix 2 PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
		TITLE	
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
		ABSTRACT	
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
		INTRODUCTION	
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
		METHODS	
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
		RESULTS	
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9

(*Contd*...)

Appendix 2 (*Continued*)

Section/topic	#	Checklist item	Reported on page #
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency	9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10, supple table-2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9
		DISCUSSION	
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11, table-1
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
		FUNDING	
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	-NA-

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendix 3 MOOSE checklist

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	-NA-
3	Description of study outcome(s)	4
4	Type of exposure or intervention used	4
5	Type of study designs used	4
6	Study population	4
Reporting of search strategy should include		
7	Qualifications of searchers (e.g., librarians and investigators)	5, appendix 1
8	Search strategy, including time period included in the synthesis and key words	5, appendix 1
9	Effort to include all available studies, including contact with authors	5
10	Databases and registries searched	5, appendix 1
11	Search software used, name and version, including special features used (e.g., explosion)	Appendix 1
12	Use of hand searching (e.g., reference lists of obtained articles)	-na-
13	List of citations located and those excluded, including justification	Appendix 1
14	Method of addressing articles published in languages other than English	-na-
15	Method of handling abstracts and unpublished studies	5
16	Description of any contact with authors	6
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	5,6
18	Rationale for the selection and coding of data (e.g., sound clinical principles or convenience)	5,6

(*Contd...*)

Appendix 3 (*Continued*)

Item No	Recommendation	Reported on Page No
19	Documentation of how data were classified and coded (e.g., multiple raters, blinding and inter-rater reliability)	5,6
20	Assessment of confounding (e.g., comparability of cases and controls in studies where appropriate)	6
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	6
22	Assessment of heterogeneity	8
23	Description of statistical methods (e.g., complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	8
24	Provision of appropriate tables and graphics	Table 1, supplemental materials
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Supplementary materials
26	Table giving descriptive information for each study included	Supplementary Table 1
27	Results of sensitivity testing (e.g., subgroup analysis)	10
28	Indication of statistical uncertainty of findings	10
Reporting of discussion should include		
29	Quantitative assessment of bias (e.g., publication bias)	10
30	Justification for exclusion (e.g., exclusion of non-English language citations)	-na-
31	Assessment of quality of included studies	Supplementary Table 2
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	11
33	Generalization of the conclusions (i.e., appropriate for the data presented and within the domain of the literature review)	11,12, 13
34	Guidelines for future research	13