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Meta-Analysis

Efficacy and safety of direct oral anticoagulants versus vitamin K antagonist for portal vein thrombosis in cirrhosis: A systematic review and meta-analysis

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ABSTRACT

Introduction and aim: Portal vein thrombosis (PVT) is associated with a higher risk of liver-related complications. Recent guidelines recommend direct-acting anticoagulants (DOAC) in patients with cirrhosis and non-tumoral PVT. However, data on the efficacy and safety of DOAC in these patients remain limited. We aim to investigate the efficacy and safety of DOAC compared to vitamin K antagonists (VKA) to treat non-tumoral PVT in patients with cirrhosis.

Methods: We performed a systematic search of six electronic databases using MeSH term and free text. We selected all studies comparing the use of DOACs with vitamin K antagonist to treat PVT in cirrhosis. The primary outcome was PVT recanalization. Secondary outcomes were and PVT progression, major bleeding, variceal bleeding and death.

Results: From 944 citations, we included 552 subjects from a total of 11 studies (10 observational and 1 randomized trial) that fulfilled the inclusion criteria. We found that DOAC were associated with a higher pooled rate of PVT recanalization (RR = 1.67, 95%CI: 1.02, 2.74, I^2 = 79%) and lower pooled risk of PVT progression (RR = 0.14, 95%CI: 0.03–0.57, I^2 = 0%). The pooled risk of major bleeding (RR = 0.29, 95%CI: 0.08–1.01, I^2 = 0%), variceal bleeding (RR = 1.29, 95%CI: 0.64–2.59, I^2 = 0%) and death (RR = 0.31, 95%CI: 0.01–9.578, I^2 = 80%) was similar between DOAC and VKA.

Conclusion: For the treatment of PVT in patients with cirrhosis, the bleeding risk was comparable between DOAC and VKA. However, DOAC were associated with a higher pooled rate of PVT recanalization. Dedicated randomized studies are needed to confirm these findings.

1. Introduction

Portal vein thrombosis (PVT) is defined as the presence of thrombus within the portal vein. It is heterogeneous with regards to its natural history and disease manifestations. PVT can be classified into completely occlusive, partially occlusive, or minimally occlusive based on the degree of occlusion in the main portal vein. Based on the time course of thrombosis, PVT can also be categorized into recent PVT (when present for less than six months) or chronic PVT (when present or persistent beyond six months) [1]. A recent PVT can be symptomatic and present with abdominal pain, fever, or ascites [2]. In patients with chronic PVT, up to 43% of cases may be asymptomatic [3]. Meanwhile, patients with chronic PVT often develop collateral venous circulation known as cavernous transformation that bypasses the obstruction.

Liver cirrhosis is an independent risk factor for the development of PVT. The prevalence of PVT increases with the severity of liver cirrhosis, ranging from 1 to 10% in compensated cirrhosis to up to 26% in decompensated cirrhosis patients [4–6]. Chronic PVT can predispose patients to portal hypertension-related complications such as ascites and variceal bleeding [7]. Not only are patients with PVT more likely to develop variceal bleeding, but these patients are at a higher risk of variceal recurrence following variceal treatment [8,9]. Furthermore, PVT is associated with a

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six-fold increased risk of liver decompensation [10], acute kidney injury, and a higher risk of long-term mortality [11,12].

Anticoagulation is recommended for cirrhosis patients with PVT, particularly among cirrhotic patients undergoing liver transplantation [13,14]. Anticoagulation improves the success of complete and partial portal vein recanalization, reduces the risk of thrombus progression, and delays the occurrence of hepatic decompensation [15,16]. Anticoagulation is also associated with a lower risk of clot progression without significantly increased risk of overall bleeding [15]. While recurrence of PVT following transplantation is associated with significantly higher mortality, anticoagulation has been shown to improve post-transplant survival [12,17].

There are practical concerns of anticoagulating cirrhosis patients using vitamin K antagonists (VKAs). The clearance of VKAs is delayed in cirrhosis patients because it is dependent on the cytochrome P450-dependent pathway. Besides, VKAs also have a narrow therapeutic range and require frequent dose titration. Their bleeding risk is also not accurately reflected using routine blood biomarkers such as international normalized ratio (INR), prothrombin time (PT) and platelet count [18]. This is because liver cirrhosis patients have unique haemostatic changes that promote clotting and bleeding simultaneously. First, impaired liver synthetic function reduces both clotting factors, pro-coagulating factors, and fibrinolytic factors [19]. Second, the production of endogenous anticoagulants within the liver such as protein C, protein S, antithrombin III and tissue plasminogen activator were also reduced. Third, haemostatic changes that promote bleeding can occur in cirrhosis patients due to low-grade systemic inflammation, which leads to increased consumption of clotting factors and promotes fibrinolysis [1,20].

Furthermore, thrombocytopenia is common in cirrhosis due to decreased thrombopoietin (TPO) production and a concurrent increase in platelet turnover and sequestration secondary to splenomegaly. For example, the bleeding risk from thrombocytopenia is buffered by a concurrent reduction in hepatic synthesis of matrix metalloproteinase ADAMST13 [21]. This promotes platelet aggregation in cirrhosis patients by increasing the half-life of von Willebrand factor [19]. These complex interactions highlight the challenges in determining the individual bleeding risk in a cirrhosis patient using routine blood biomarkers (INR, PT, or platelet count), which do not fully account for the haemostatic changes that promote clotting.

Meanwhile, there is growing interest in using direct oral anticoagulants (DOACs) because of their ease of monitoring without significant drug-drug interactions, including patients with hereditary thrombophilia [22]. Current recommendations of using DOAC in PVT are based on limited evidence [1]. The pharmacokinetics of DOAC is affected by liver function, albeit to a lesser extent [19]. While emerging evidence supports DOAC as a safe alternative to VKA in cirrhosis patients with atrial fibrillation [23,24], data on the efficacy and safety of DOAC among cirrhosis patients with PVT remains limited. Not only were cirrhosis patients systematically excluded from clinical trials comparing DOAC and VKA [25,26], but the experience on DOAC in PVT is also largely derived from small retrospective studies [27,29]. This gap is further confounded by wide variation in terms of their inclusion criteria, treatment duration, and definitions of bleeding outcomes [10]. Given the paucity of data to address this unmet need, it is timely and clinically relevant to systematically review the safety and efficacy of DOACs versus VKAs in cirrhosis patients with non-tumoral PVT.

2. Methods

2.1. Eligibility criteria

This meta-analysis aims to compare the efficacy and safety of DOACs versus VKA to treat non-tumoral PVT in patients with liver cirrhosis. Cirrhosis was diagnosed based on either histological, radiological, or clinical features of liver cirrhosis. All types of DOAC, regardless of their dose and duration, were included. Our primary outcome was the pooled risk of either complete or partial portal vein recanalization, major bleeding, variceal bleeding as well as death. Complete or partial recanalization is defined as a complete disappearance or reduction in the degree of PVT occlusion following anticoagulation. We adopted the ISTH definition of major bleeding as fatal bleeding or symptomatic bleeding in a critical area or organ or bleeding causing a fall in hemoglobin level of 2 g/dL or more or leading to transfusion of two or more units of whole blood or red cells [30].

2.2. Search strategy

We followed the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines for data extraction and reporting [31]. All potential literature were identified from a comprehensive search of six electronic databases, namely PubMed/MEDLINE, EMBASE, Cochrane Library, Scopus, and Web of Science and ClinicalTrial.gov from the beginning of record up to 30th May 2021, with the help of an experienced medical librarian. There was no restriction on language, geography, publication dates and publication status (full text or abstract). The search keywords included a combination of MeSH terms and free texts using the following keywords: 'direct oral anticoagulants', 'novel oral anticoagulants', 'portal venous thrombosis', 'portal vein thrombosis' and 'cirrhosis' (*Supplementary Table 1*). All references of the included studies were manually searched for additional studies.

2.3. Study selection

In this meta-analysis, we included all randomized and non-randomized studies regardless of language, geography, publication dates and publication status that fulfilled the following inclusion criteria: (1) Adult cirrhosis patients with non-tumoral portal vein thrombosis, (2) subjects received either VKA or DOAC as oral anticoagulation therapy and (3) reported outcome data on either portal vein recanalization, bleeding, or death. We excluded (1) review articles, editorials, and guidelines and (2) animal or pediatric studies. Three authors independently reviewed all titles and abstracts of the studies identified in the primary search. After excluding all studies that did not fulfill the pre-defined inclusion criteria, we reviewed the full texts of all short-listed studies to determine if they contained relevant information. Any discrepancy in the article selection was resolved by consensus with the senior author.

2.4. Data extraction

We extracted data on the demographic of study participants (age, sample size, etiology of CLD, and severity of liver cirrhosis) and study design. We extracted data on the types, duration and class of anticoagulants (VKA or DOAC). Outcome data such as PVT recanalization and bleeding were also extracted based on predefined definitions. The data from each study were independently extracted into a standardized form by two authors. In the event of missing data during data extraction, the corresponding authors were contacted through email correspondence.

2.5. Risk of bias assessment

Two authors independently reviewed all included studies to assess their risk of bias using the Newcastle-Ottawa scale for non-randomized studies and Cochrane Risk of Bias tools for randomized trials [32,33]. The scoring consists of 10 questions as summarized in *Supplementary Table 2*. We consider a total score of 7 and above,

4 to 6 and ≤ 3 as low risk of bias, moderate risk of bias, and high risk of bias, respectively.

2.6. Data synthesis and analysis

We used Review Manager Software version 5.3 (The Nordic Cochrane center, The Cochrane Collaboration, 2014) to perform this meta-analysis. The effect measures were presented in pooled relative risk ratio (RR) and 95% confidence interval (95%CI). We consider a p-value of < 0.05 to be statistically significant. The statistical heterogeneity was evaluated using the I^2 statistic. We defined substantial heterogeneity across study as low, moderate, substantial, and considerable with an I^2 value of <30%, 31% to 60%, 61% to 74%, and >75% [34]. We used the random-effects model as we anticipate heterogeneity among the included studies. We performed sensitivity analysis by repeating our analysis using odds ratio as well as fixed-effect model. Finally, we calculated the number needed to treat (NNT) to estimate the potential effect of DOAC compared to VKA for the treatment of PVT.

3. Results

3.1. Search result and population characteristics

Among the initial 944 citations identified using our search strategy, we identified a total of 51 relevant studies for full-text review. Of these, we excluded 40 studies for the following reasons: anticoagulation for atrial fibrillation ($n = 14$), study subjects were non-cirrhotic ($n = 9$), ongoing clinical trials ($n = 7$), inadequate information ($n = 5$), and study outcome not available ($n = 5$). Finally, a total of eleven studies met our inclusion criteria [27–29,35–42].

3.2. Characteristics and quality of the studies

The characteristics of all eleven studies involving 552 subjects (217 received DOAC, 335 received VKA) are summarized in Table 1 [27–29,35–42]. There was one randomized controlled trial [29] and ten retrospective cohort studies [27,28,35–42] included from the United States ($n = 6$), Japan ($n = 2$), Austria ($n = 1$), Switzerland ($n = 1$) and Egypt ($n = 1$). All studies were published as full manuscripts except for three, which were abstracts [37,38,40]. Eight studies published as full manuscripts were considered to be of low risk of bias. The remaining three studies were abstracts and were assessed to be at moderate risk of bias.

The mean age of study subjects ranged from 41 to 69 years old. The proportion of subjects with baseline oesophageal varices or antiplatelet were 20.2% and 7.4%, respectively. Three studies included patients with Child-Turcotte-Pugh (CTP) class C [28,39,40]. Total follow-up duration ranged from 3 to 12 months. The choice of DOACs included rivaroxaban (5 studies) [27,29,35–37], apixaban (5 studies) [27,29,35,37,41], edoxaban (3 studies) [28,40,41] and dabigatran (2 studies) [27,41]. Duration of anticoagulation ranged between 3.2 to 19.0 months. The overall pooled rate of PVT recanalization was 46% (95%CI: 57.1%−70.6%). The overall pooled risk of major bleeding and death was 7.9% (95%CI: 4.3%−13.1%) and 10.2% (95%CI: 6.0%−15.8%), respectively.

3.3. Efficacy of direct oral anticoagulants

3.3.1. PVT recanalization

A total of five studies compared the outcome of PVT recanalization among cirrhotic patients who received anticoagulation [28,29,37,38,40]. The pooled rate of PVT recanalization in DOAC and VKA groups were 87.3% (95%CI: 79.0%−93.3%) and 44.1% (95%CI: 34.7%−53.9%), respectively. Compared to VKA, DOAC was associated with a higher rate of PVT recanalization, with substantial heterogeneity (RR = 1.67, 95%CI: 1.02, 2.74, $I^2 = 79\%$) (Fig. 1). The finding was sensitive to study design, where the benefit of DOAC was observed within the RCT (RR = 2.19, 95%CI: 1.56, 3.07), but not among the cohort studies (RR = 1.49, 95%CI: 0.76, 2.90, $I^2 = 80\%$).

3.3.2. PVT progression

A total of three studies compared the risk of PVT progression among cirrhotic patients on DOAC versus cirrhotic patients on VKA [28,29,37]. The overall pooled risk of PVT progression while on anticoagulation was 12.9% (95%CI: 8.2%−19.0%). DOAC was associated with a significantly lower risk of PVT progression than VKA (RR = 0.14, 95%CI: 0.03–0.57, $I^2 = 0\%$) (Fig. 2).

3.3.3. Major bleeding and variceal bleeding

Overall, seven studies [27–29,35,36,40,41] reported the bleeding risk of anticoagulation in cirrhotic patients with PVT. DOAC was associated with a lower pooled risk of major bleeding than VKA (RR = 0.29, 95%CI: 0.08–1.01, $I^2 = 0\%$) (Fig. 3). The overall pooled risk of variceal bleeding was 18.7% (95%CI: 14.5%−23.4%), which was similar between DOAC and VKA (RR = 1.29, 95%CI: 0.64–2.59, $I^2 = 0\%$) (Fig. 4). The pooled risk of death was similar between DOAC and VKA (RR = 0.31, 95%CI: 0.01–9.578, $I^2 = 80\%$) with substantial heterogeneity (Fig. 5).

3.4. Sensitivity analysis

We performed subgroup analysis based on the fixed-effect models and found that our findings remained robust for all outcomes.

3.5. Publication bias

There was no evidence of publication bias on studies reporting PVT recanalization based on visual inspection of the funnel plot (*Supplementary Fig. 1*).

4. Discussion

In this meta-analysis of eleven studies with 552 cirrhosis patients, we showed that DOAC is a reasonable alternative for the treatment of PVT. Compared to VKA, DOAC were associated with a higher pooled rate of PVT recanalization and a lower pooled rate of PVT progression. The safety profile between DOAC and VKA was comparable in terms of the risk of major bleeding, variceal bleeding, and death in the setting of chronic PVT. Considering the limitations of VKA regarding their safety and ease of monitoring, our findings have important implications in informing physicians on the efficacy and safety when considering DOAC in cirrhosis patients with chronic PVT.

Our findings expand the understanding of the safety profile of DOAC among cirrhosis patients, particularly in patients with chronic PVT. Recently, Valeriani et al. showed that anticoagulation in cirrhosis patients with PVT significantly improve the recanalization rate and reduce thrombus progression, as compared to cirrhosis patients without anticoagulation [43]. These findings are clinically relevant because PVT predisposes cirrhosis patients to future liver decompensation and death [8]. While prior studies have investigated the use of DOAC versus traditional anticoagulants among cirrhosis patients in the setting of atrial fibrillation and venous thromboembolism [44,45], data on the efficacy and safety of DOAC in chronic PVT remains scarce [1]. A recent meta-analysis by Chen et al. suggested that DOAC may be superior to VKA for treating cirrhosis patients with PVT [46]. However, the definition

Table 1
Study and population characteristics.

Author, year, references	Country	Study design	Sample size	Age in year (mean/SD; median/IQR)	Population	Child-Turcotte-Pugh Class A/B/C (*n*)	Types of Anticoagulation	DOAC (n)	Duration of anticoagulation (mean, months)
De Gottardi, 2016	Switzerland	Retrospective cohort study	22	65.3 (12.8)	Cirrhotic patients with PVT	NA	Apixaban, rivaroxaban, dabigatran	22	9.25 (6.90)
Intagliata, 2016	USA	Retrospective cohort study	39	DOAC: 57 (50–64) Warfarin: 60 (55–64)	Cirrhotic patients with PVT	DOAC: 9/11/0 Warfarin: 9/10/0	Apixaban, rivaroxaban	20	DOAC:8.8 VKA: 15.7
Hum, 2017	USA	Retrospective cohort study	45	DOAC: 61 (26–90) Warfarin: 58 (34–80)	Cirrhosis patients with AF, VTE, PVT or DVT	DOAC: 11/12/4 Warfarin: 7/9/2	Apixaban, rivaroxaban	27	DOAC: 11.3 VKA: 8
Nagaoka, 2017	Japan	Retrospective cohort study	50	DOAC: 69 (53–74) Warfarin: 67 (24–83)	Cirrhotic patients with PVT	DOAC: 15/5/0 Warfarin: 15/10/5	Edoxaban vs warfarin	20	DOAC: 6 VKA: 6
Hanafy, 2018	Egypt	RCT	80	DOAC: 46 ± 5 Warfarin: 41.3 ± 2.3	HCV-related compensated cirrhosis with PVT	CTP score: 10.2 ± 1.3	Rivaroxaban vs warfarin	40	DOAC: 4.3 VKA: 3.2
Scheiner, 2018	Austria	Retrospective cohort study	10	50 ± 18	Cirrhotic patients with PVT	10/0/0	Edoxaban, apixaban, rivaroxaban, dabigatran	10	9.2
Yuko, 2018	Japan	Retrospective cohort study	65	NA	Cirrhotic patients with PVT	NA	Edoxaban vs warfarin	35	DOAC: 6 VKA: 6
Irina, 2019	USA	Retrospective cohort study	27	NA	Cirrhotic patients with PVT	NA	NA	NA	NA
Davis, 2020	USA	Retrospective cohort study	167	DOAC: 59 (52–67) Warfarin: 63 (58–72)	Cirrhosis patients received anticoagulation	Overall: 78/64/10	Apixaban, rivaroxaban & dabigatran vs warfarin	57	NA
Ilcewicz, 2020	USA	Retrospective cohort study	33	51 ± 16	Patients with PVT	MELD (10.5; range: 8–25)	Apixaban & rivaroxaban vs warfarin	13	3
Joseph, 2020	USA	Retrospective cohort study	16	DOAC: 61 (59–61) Warfarin: 55 (54–60)	Cirrhotic patients with acute PVT	DOAC: 3/2/0 Warfarin: 2/8/1	Not specified	5	3–6

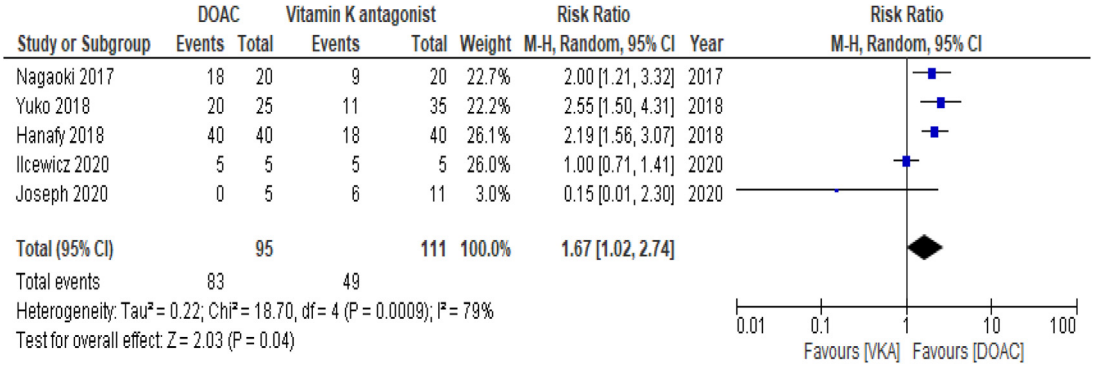

Fig. 1. Pooled rate of portal vein thrombosis recanalization (partial or complete).

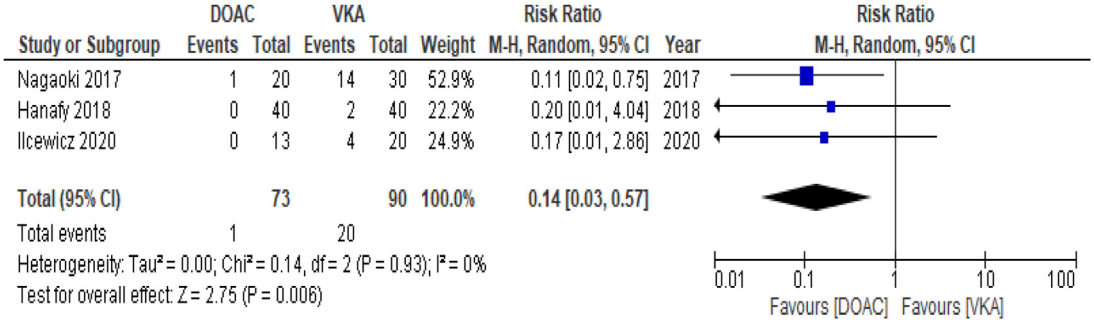

Fig. 2. Pooled risk of portal vein thrombosis progression.

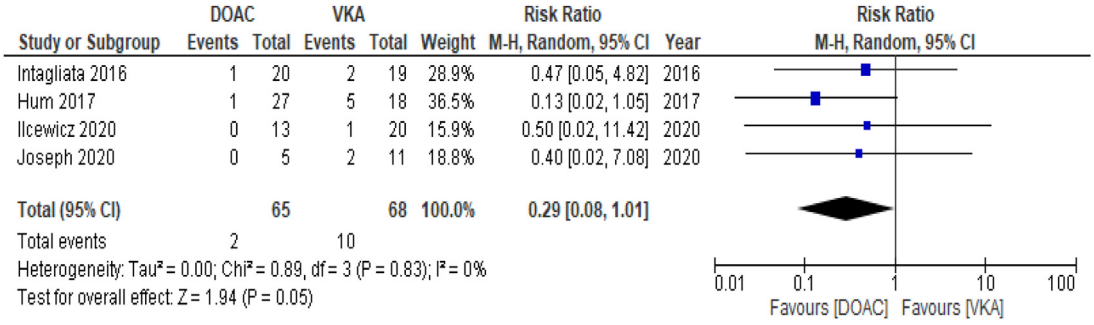

Fig. 3. Pooled risk of major bleeding.

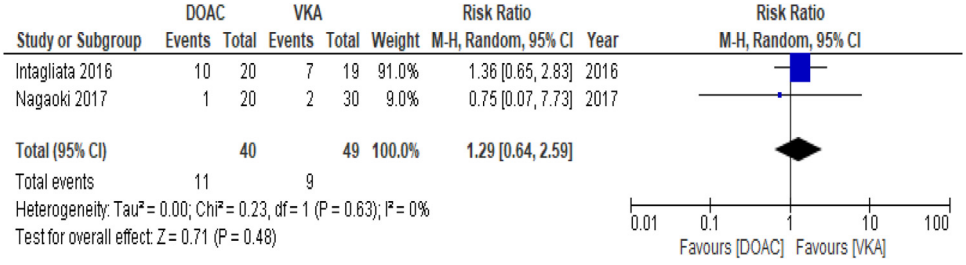

Fig. 4. Pooled risk of variceal bleeding.

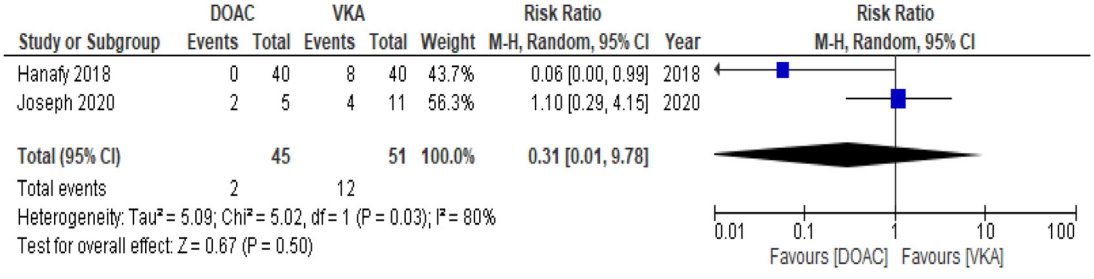

Fig. 5. Pooled risk of death.

of bleeding was inconsistent, and only three studies directly comparing VKA and DOAC were included. This updated meta-analysis followed a pre-defined, validated definition of severe bleeding for outcome reporting [30]. Furthermore, we also included five additional studies [27,36–38,40] than Chen et al. through our systematic search.

There are several strengths of this meta-analysis. Firstly, our study provided a direct comparison between DOAC and VKA for chronic PVT in cirrhosis patients. With the help of an experienced medical librarian, we comprehensively searched six electronic databases using pre-defined criteria and included five studies [27,36–38,40]. Our study is more comprehensive than the previous studies, which either did not evaluate comparative efficacy and safety of VKA versus DOAC [47,48] or included fewer studies [46,49]. To mitigate reporting biases arising from discrepancy in reporting bleeding outcomes from previous studies, we adopted a validated and standardized definition for major bleeding based on the International Society on Thrombosis and Haemostasis (ISTH) [30]. Data extraction was independently performed using a predefined template to ensure consistency in reporting outcomes. All corresponding authors were contacted for any missing data that was not reported in the original study.

Our meta-analysis was limited by potential selection bias among the non-randomized studies. As the study outcome was not stratified based on CTP class, we cannot perform subgroup analysis to compare the outcome between DOAC and VKA according to the severity of liver cirrhosis. Furthermore, the use of DOAC is not recommended in patients with Child-Turcott-Pugh (CTP) stage C cirrhosis and those presenting with significantly decreased creatinine clearance. For this reason, the results of this study apply to CTP- A and CTP-B patients. More safety data is required among decompensated cirrhosis patients awaiting liver transplantation. Our meta-analysis was limited by the number of studies included because DOAC was not licenced in advanced cirrhosis patients. As we had conducted a comprehensive search of six electronic databases and attempted to identify gray literature with the help of a medical librarian, we believe the small number of studies reflects the paucity of current data rather than a limitation of our existing study. We recognized that substantial heterogeneity exists among the included studies due to clinical heterogeneity in terms of treatment dosing, duration, follow-up, and study population. Lastly, we are unable to perform subgroup analysis based on the chronicity extent, and severity of PVT due to limited data.

In conclusion, compared to VKA, DOAC were associated with a higher rate of portal vein recanalization and a lower risk of PVT progression. The risk of major bleeding, variceal bleeding and death were similar between DOAC and VKA in the setting of chronic PVT. Due to limited data among patients with decompensated cirrhosis, further randomized studies are warranted to compare the safety and efficacy of DOAC for PVT, particularly in patients awaiting liver transplantation where the benefits of treating chronic PVT were best demonstrated.

Declaration of Competing Interest

All authors declared that we had **no** conflict of interest related to this study titled “Efficacy and safety of direct-acting oral anticoagulants versus vitamin K antagonists for cirrhosis patients with portal vein thrombosis: a systematic review and meta-analysis”

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2021.07.039.

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