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Review Article

It's time for head-to-head trials with direct oral anticoagulants

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ABSTRACT

Direct oral anticoagulants (DOACs) have become the recommended first choice anticoagulant agent for treatment of acute venous thromboembolism (VTE) in non-cancer patients and are increasingly prescribed worldwide. They have not only intrinsic advantages, such as rapid onset of action and wide therapeutic windows, but also a lower risk of major, intracranial and fatal bleeding in VTE patients compared to vitamin K antagonists. Even though DOACs are often referred to as uniform drug class, there is growing evidence that each DOAC has a specific risk profile. Indirect comparisons and retrospective cohort studies suggest that apixaban may be associated with a lower risk of major bleeding than other DOACs, but there are no head-to-head trials with DOACs. Therefore, current guidelines do not recommend one DOAC over another and the choice of a specific DOAC is mainly based on physician and patient preferences, reimbursement and availability. Retrospective cohort studies and VTE registries are important to identify potential differences in efficacy and safety between DOACs; but they are methodologically too limited to inform the optimal choice of oral anticoagulant agent. Randomized controlled trials are crucial to inform sound treatment recommendations, because proper randomization is the key to unprejudiced treatment allocation and minimization of unmeasured and unknown confounding. Given increasing evidence of differences in safety profiles of DOACs from indirect comparisons and observational studies, it's time for head-to-head trials with DOACs.

1. Introduction

The introduction of direct oral anticoagulants (DOACs), including direct inhibitors of thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban, edoxaban), has changed the landscape of treatment of acute venous thromboembolism (VTE). Because of intrinsic advantages, such as rapid onset of action and wide therapeutic windows, and a lower risk of bleeding compared to vitamin K antagonists (VKAs) (Table 1), DOACs have become the first choice anticoagulant agents for treatment of acute VTE in non-cancer patients [1–3]. As there are no head-to-head trials with DOACs, current guidelines do not recommend one DOAC over another and the choice of a specific DOAC is often based on physician and patient preferences, availability and reimbursement.

DOACs are often referred to as uniform drug class, but pharmacokinetic properties differ between each DOAC and study design varied moderately across phase III trials. Furthermore, indirect comparisons and a recent retrospective cohort study suggest that apixaban may be associated with the lowest risk of bleeding [4–6]. While these studies are not appropriate to inform the optimal choice of anticoagulant agent, they are hypothesis-generating and contribute to the rationale for direct DOAC comparison trials.

This narrative review focuses on DOACs for treatment of VTE in non-cancer patients, studies evaluating different DOACs, their limitations, and the rationale for head-to-head trials with DOACs. In addition, we explore the design of pragmatic trials as an option for head-to-head comparisons.

2. Direct oral anticoagulants

DOACs were developed to overcome challenges of VKA treatment such as drug monitoring, frequent dosing adjustments, and food and drug interactions. An additional advantage to using rivaroxaban and apixaban is eliminating the necessity of low-molecular-weight heparin lead-in at treatment initiation. Compared to warfarin, DOACs have a

Abbreviations: CI, confidence interval; CrI, credible interval; DOAC, direct oral anticoagulant; HR, hazard ratio; RCT, randomized controlled trial; VKA, vitamin K antagonist; VTE, venous thromboembolism

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Table 1
Risk of bleeding in phase III trials of direct oral anticoagulants for treatment of acute VTE in non-cancer patients.

Source	Intervention	Control	Hazard ratio/relative risk of recurrent VTE (95% CI)	Hazard ratio/relative risk of bleeding (95% CI)
RE-COVER [8]	Dabigatran (n = 1274)	VKA, INR 2–3 (n = 1265)	HR, 1.10 (0.65–1.84)	MB: HR, 0.82 (0.45–1.48) CRNMB: NR CRB: HR, 0.63 (0.47–0.84)
RE-COVER II [9]	Dabigatran (n = 1279)	VKA, INR 2–3 (n = 1289)	HR, 1.08 (0.64–1.80)	MB: HR, 0.69 (0.36–1.32) CRNMB: NR CRB: HR, 0.62 (0.45–0.84)
EINSTEIN-DVT [10]	Rivaroxaban (n = 1731)	VKA, INR 2–3 (n = 1718)	HR, 0.68 (0.44–1.04)	MB: HR, 0.65 (0.33–1.30) CRNMB: NR CRB: HR, 0.97 (0.76–1.22)
EINSTEIN-PE [11]	Rivaroxaban (n = 2419)	VKA, INR 2–3 (n = 2413)	HR, 1.12 (0.75–1.68)	MB: HR, 0.49 (0.31–0.79) CRNMB: NR CRB: HR, 0.90 (0.76–1.07)
AMPLIFY [12]	Apixaban (n = 2691)	VKA, INR 2–3 (n = 2704)	RR, 0.84 (0.60–1.18)	MB: RR, 0.31 (0.17–0.55) CRNMB: RR, 0.48 (0.38–0.60) CRB: RR, 0.44 (0.36–0.55)
Hokusai-VTE [13]	Edoxaban (n = 4118)	VKA, INR 2–3 (n = 4122)	HR, 0.89 (0.70–1.13)	MB: HR, 0.84 (0.59–1.21) CRNMB: HR, 0.80 (0.68–0.93) CRB: HR, 0.81 (0.71–0.94)

Abbreviations: CI, confidence interval; CRB, clinically relevant bleeding; CRNMB, clinically relevant non-major bleeding; HR, hazard ratio; INR, international normalized ratio; MB, major bleeding; RR, relative risk; VKA, vitamin K antagonist; VTE, venous thromboembolism; NR, not reported.

fast onset of action with a time to peak serum concentration of 2–4 h (vs 72–120 h for warfarin) and a short half-life (7–17 h vs 20–60 h for warfarin) [7]. Both properties simplify initiation of treatment as well as interruption of oral anticoagulation if needed. Wide therapeutic windows, fewer drug-drug interactions and no drug-food interactions allow for administration of fixed DOAC doses and minimizes the need for laboratory monitoring [7]. DOACs have not yet been studied in patients with severe renal impairment and thus, VKAs remain the treatment of choice for patients with a creatinine clearance of less than 25–30 mL/min. The ongoing VERDICT study aims to evaluate whether reduced doses of apixaban and rivaroxaban are non-inferior to standard of care (i.e., parenteral anticoagulant plus VKA) for treatment of VTE in patients with moderate to severe renal insufficiency (ClinicalTrials.gov identifier: NCT02664155).

2.1. Direct oral anticoagulants for treatment of venous thromboembolism

2.1.1. Acute VTE treatment

DOACs have been approved for treatment of acute VTE based on 6 phase III trials including over 27,000 patients (Table 1) [8–13]. All trials had a non-inferiority design comparing a DOAC to low-molecular-weight heparin followed by standard-intensity VKA. Each DOAC has been proven non-inferior to VKAs for reduction of recurrent VTE (Table 1). Compared to VKAs, rivaroxaban in patients with pulmonary embolism, and apixaban, were associated with a lower risk of major bleeding, and dabigatran, apixaban and edoxaban with a lower risk of clinically relevant bleeding, defined as major bleeding or clinically relevant non-major bleeding (Table 1). In meta-analyses of the phase III trials, DOACs were associated with a lower risk of major bleeding than VKAs (relative risk, 0.62; 95% confidence interval [CI], 0.45–0.85), with no difference in risk of recurrent VTE (relative risk 0.91, 95% CI, 0.79 to 1.06) [14], which reinforced the superior safety profile without difference in VTE recurrence risk as a DOAC class effect [14,15]. Criteria for diagnosing recurrent VTE and major bleeding events were identical across all phase III studies while clinically relevant non-major bleedings were not standardized across trials. In every trial, outcomes were adjudicated by an independent committee chaired by the same person. Even though there were many similarities in design and conduction of the phase III trials, some differences deserve attention. Dabigatran, apixaban and edoxaban were assessed in a double-blind double-dummy study design, while rivaroxaban was studied open-label. Both designs provide advantages and disadvantages in evaluating a new anticoagulant drug and differences in design across phase III trial led to intense discussion [16]. While blinding aims to ensure minimization of performance, attrition and detection bias, potential disadvantages include a decrease in external validity due to complex study interventions. The latter is particularly the case for double-blind double-dummy anticoagulation trials including VKA as comparator that requires frequent dose adjustments based on laboratory tests [17]. In addition to variations in study design, eligibility criteria across phase III trials differed slightly. Even if only moderate, such differences can impact study outcomes [18].

2.1.2. Extended VTE treatment

Compared to placebo, extended treatment of VTE with VKA reduces the risk of recurrent VTE (odds ratio, 0.15; 95% credible interval [CrI], 0.08–0.24) but is associated with an increased risk of major bleeding (odds ratio, 4.42; 95% CrI, 1.99–12.24) [19]. To address the higher risk of bleeding, the ELATE trial compared treatment with low-intensity VKA (target international normalized ratio, 1.5–2.0) to standard-intensity VKA [20]. While the risk of major bleeding did not differ between the treatment arms (hazard ratio, 1.2; 95% CI, 0.4–3.0), low-intensity VKA was associated with a higher risk of recurrent VTE (hazard ratio, 2.8; 95% CI, 1.1–7.0) [20]. Naturally, the efficacy and safety of DOACs were next evaluated in extended VTE treatment.

The use of DOACs for extended treatment of VTE is supported by 5 dedicated trials and 1 post-hoc analysis of the Hokusai-VTE study (Table 2). Study designs of phase III DOAC trials for extended VTE treatment varied considerably more than those for acute treatment. Direct oral anticoagulants were studied in non-inferiority trials against standard-intensity VKA, and in superiority trials against aspirin and placebo. The RE-MEDY study comparing dabigatran to standard-intensity VKA is the only trial designed to specifically evaluate a DOAC against VKAs during extended treatment. In addition to dabigatran, a post-hoc analysis of the Hokusai VTE trial explicitly reports outcomes of edoxaban versus standard-intensity VKA in patient treated beyond the acute phase of 3 months. Both dabigatran and edoxaban were non-inferior to VKAs for prevention of recurrent VTE and associated with a

Table 2
Risk of bleeding in phase III trials of direct oral anticoagulants for treatment of extended VTE in non-cancer patients.

Source	Intervention	Control	Hazard ratio/relative risk of recurrent VTE (95% CI)	Hazard ratio/relative risk of bleeding (95% CI)
RE-MEDY [21]	Dabigatran, 150 mg bid (n = 1430)	VKA, INR 2–3 (n = 1426)	HR, 1.44 (0.78–2.64)	MB: HR, 0.52 (0.27–1.02) CRNMB: NR CRB: HR, 0.54 (0.41–0.71)
RE-SONATE [21]	Dabigatran, 150 mg bid (n = 681)	Placebo (n = 662)	HR, 0.08 (0.02–0.25)	MB: Not estimable CRNMB: NR CRB: HR, 2.92 (1.52–5.60)
EINSTEIN-EXT [10]	Rivaroxaban, 20 mg/d (n = 602)	Placebo (n = 594)	HR, 0.18 (0.09–0.39)	MB: Not estimable CRNMB: NR CRB: HR, 5.19 (2.3–11.7)
EINSTEIN-CHOICE [24]	Rivaroxaban, 20 mg/d (n = 1107)	Aspirin, 100 mg/d (n = 1131)	HR, 0.34 (0.20–0.59)	MB: HR, 2.01 (0.50–8.04) CRNMB: HR, 1.53 (0.87–2.69) CRB: HR, 1.59 (0.94–2.69)
	Rivaroxaban, 10 mg/d (n = 1127)	Aspirin, 100 mg/d (n = 1131)	HR, 0.26 (0.14–0.47)	MB: HR, 1.64 (0.39–6.84) CRNMB: HR, 1.09 (0.59–2.00) CRB: HR, 1.16 (0.67–2.03)
AMPLIFY-EXT [23]	Apixaban, 5 mg bid (n = 813)	Placebo (n = 829)	RR, 0.20 (0.11–0.34)	MB: RR, 0.25 (0.03–2.24) CRNMB: RR, 1.82 (1.05–3.18) CRB: RR, 1.62 (0.96–2.73)
	Apixaban, 2.5 mg bid (n = 840)	Placebo (n = 829)	RR, 0.19 (0.11–0.33)	MB: RR, 0.49 (0.09–2.64) CRNMB: RR, 1.29 (0.72–2.33) CRB: RR, 1.20 (0.69–2.10)
Post-hoc analysis Hokusai-VTE [22]	Edoxaban, 60 mg/d[a] (n = 3633)	VKA, INR 2–3 (n = 3594)	HR, 0.97 (0.70–1.40)	MB: HR, 0.45 (0.22–0.92) CRNMB: HR, 1.06 (0.83–1.35) CRB: HR, 0.97 (0.77–1.22)

Abbreviations: bid, bis in die; CI, confidence interval; CRB, clinically relevant bleeding; CRNMB, clinically relevant non-major bleeding; HR, hazard ratio; INR, international normalized ratio; MB, major bleeding; RR, relative risk; VKA, vitamin K antagonist; VTE, venous thromboembolism; NR, not reported.
[a] Edoxaban 30 mg/d if creatinine clearance of 30 to 50 mL/min or body weight below 60 kg.

lower risk of major bleeding than VKAs (Table 2) [13,21,22]. Compared to placebo, rivaroxaban, dabigatran and apixaban significantly reduced the risk of recurrent VTE during extended treatment, without showing an increased risk of major bleeding (Table 2) [10,21,23]. In contrast to VKA, rivaroxaban and apixaban can be given at reduced doses (i.e., rivaroxaban 10 mg daily and apixaban 2.5 mg twice daily) for secondary prevention and extended treatment of VTE, because reduced doses are superior to placebo and aspirin and appear to be as efficacious as standard doses [23,24].

Following phase III DOAC trials and recommendations of DOACs over VKAs for acute VTE treatment by the 2016 American College of Chest Physicians and 2014 and 2017 European Society of Cardiology guidelines [1–3], there was rapid and continued uptake of DOAC use in clinical practice [25–27]. The most frequently used DOACs for treatment of acute VTE are rivaroxaban and apixaban given their simplicity as single drug treatments (i.e., no need for parenteral low-molecular-weight heparin lead-in) [25,26].

2.2. Comparison of direct oral anticoagulants in network meta-analyses and observational studies

Even though DOACs are usually referred to as a uniform drug class, there is growing evidence that the risk of bleeding may differ between specific DOACs. A network meta-analysis of 45 randomized controlled trials (RCTs) comparing 8 anticoagulation options for acute VTE treatment showed that while there was no difference in risk of recurrent VTE between DOACs, rivaroxaban and apixaban were associated with the lowest risk of major bleeding (HR, 0.55; 95% CrI, 0.35–0.89 for rivaroxaban compared to VKA; HR, 0.31; 95% CrI, 0.15–0.62 for apixaban compared to VKA) [4]. Apixaban was associated with a significantly lower risk of major bleeding than dabigatran (HR, 0.42; 95% CrI, 0.17–0.99) and edoxaban (HR, 0.37; 95% CrI, 0.15–0.89) [4]. Indirect comparison with rivaroxaban indicated also a lower major bleeding risk for apixaban but the difference did not reach statistical significance (HR, 0.56; 95% CrI, 0.24–1.33) [4]. Similar results for the risk of major bleeding associated with different DOACs were shown in another Bayesian network-meta-analysis including all 6 phase III DOACs trials for acute VTE treatment [5]. Furthermore, apixaban was associated with a significantly lower risk of clinically relevant non-major bleeding than rivaroxaban (relative risk, 0.47; 95% CrI, 0.38–0.68) and edoxaban (relative risk, 0.59; 95% CrI, 0.45–0.78); comparison of apixaban with dabigatran showed no difference in clinically relevant non-major bleeding (relative risk, 0.80; 95% CrI, 0.57–1.12) [5]. When comparing the risk of clinically relevant bleeding, defined as composite of major bleeding and clinically relevant non-major bleeding, apixaban was superior to dabigatran, rivaroxaban, and edoxaban [5]. Network meta-analyses do not indicate superiority of one DOAC over another for reduction in recurrent VTE during extended treatment [28]. Indirect comparisons of DOACs regarding bleeding risk are limited by few events in the pivotal RCTs. Overall, there were only 44 major bleeds in 9233 patients on DOACs in all phase III DOAC trials for extended VTE treatment [10,21–24]. Accordingly, credibility intervals in network meta-analyses are large and preclude judgment on statistical significance [28,29].

A recent retrospective cohort study including 15,254 patients with acute VTE from the Truven Health MarketScan commercial and Medicare Supplement claims databases support the findings of the network meta-analyses [6]. After propensity score matching, apixaban was associated with a lower risk of major bleeding than rivaroxaban (HR, 0.54; 95% CI, 0.37–0.82) [6]. Interestingly and in contrast to previous network meta-analyses [4,5], this study showed a lower risk of recurrent VTE in patients on apixaban compared to those on rivaroxaban (HR, 0.37; 95% CI, 0.24–0.55) [6]. The main limitations of this large database study are the risk of differential outcome

misclassification, indication bias, and residual confounding as outlined below.

3. Why are direct comparison randomized controlled trials needed?

If not supported by RCTs, evidence from network meta-analysis and observational studies must be understood as hypothesis-generating. So called real-world studies are important to recognize post-marketing safety issues and can contribute to the rationale and need of future trials but they are methodologically limited to provide practice changing treatment comparisons [30]. The main issue of such studies is residual confounding despite sophisticated statistical methods which allow for adjustment of known and measured confounders [31,32]. Proper randomization not only balances patient characteristics including measured and unmeasured confounders between all study arms but also ensures that investigators have no a priori knowledge to which treatment group the next patient will be assigned (i.e., concealed allocation). Knowledge of treatment allocation prior to patient enrolment may introduce selection bias, an issue than could not be completely adjusted for in the above-mentioned retrospective study comparing apixaban and rivaroxaban and is one of several potential sources of residual confounding in this study.

A core assumption for valid indirect comparisons is similarity of studies included in a network meta-analysis. For example, differences in eligibility criteria can lead to different outcomes and subsequently, biased estimates in network meta-analysis. A post-hoc analysis of the EINSTEIN trials suggested that 31% of patients enrolled in the EINSTEIN studies would have been ineligible in the AMPLIFY trial [18]. Comparison between eligible and ineligible patients based on the post-hoc assessment showed significant differences in outcomes. While the risk of recurrent VTE and major bleeding did not differ between rivaroxaban and VKA in patients theoretically ineligible for the AMPLIFY trial, rivaroxaban was associated with a lower risk of VTE recurrence and major bleeding than VKA in patients eligible for both the EINSTEIN and AMPLIFY trials [18]. Even though this study has its own limitations, it helps illustrate that uncertainties introduced by between-study differences such as variable eligibility criteria or heterogeneous follow-up duration, preclude judgment on superiority of one DOAC over another based on across study comparisons in network meta-analysis.

Given the limitations of existing evidence, high-quality RCTs comparing DOACs are needed before recommendations regarding the choice of one DOAC over another can be made.

3.1. Pragmatic trials

While registries and retrospective cohort studies cannot replace traditional RCTs, pragmatic RCTs are a viable alternative depending on study question. The distinction between exploratory and pragmatic trials was first described in 1967 [33]. Exploratory RCTs are traditional RCTs which aim to reveal a biological effect in idealized conditions. In contrast, pragmatic RCTs aim to provide widely generalizable results by comparing treatments under practical conditions. As per Schwartz and Lellouch, exploratory trials aim at understanding and pragmatic trials aim at decision [33]. The need for pragmatic RCTs that inform clinical decisions has been increasingly acknowledged over the past decades by scientists and funding agencies [34–38]. Because one third of self-labelled pragmatic RCTs on drug or biologic agents include study features that are hardly compatible with pragmatism such as single-center or placebo-controlled designs, investigators and editors should use standardized methods to assess the degree of pragmatism before labelling an RCT as pragmatic [39]. The most widely-accepted tool is the PRagmatic-Exploratory Continuum Indicator Summary 2 (PRECIS-2) which has been developed by trialists, clinicians and policymakers [40]. It has 9 domains which are scored from 1 (very exploratory) to 5 (very pragmatic) (Table 3). As the name of the tool indicates, there is a continuum between exploratory and pragmatic trials or their design features and rarely a trial is purely exploratory or pragmatic in every aspect. Each domain of PRECIS-2 is assessed independently, and as such, the tool should be mainly used to help identify design choices that alter the trial's nature as being more pragmatic or exploratory. Publication of the PRECIS-2 assessment and reporting guided by the CONSORT statement extension for pragmatic trials should be encouraged to help readers appraise the reasons why the study claims to be pragmatic and to provide practice-based evidence [39,41].

4. Ongoing trials

The lack of head-to-head trials with DOACs for treatment of VTE offers a great opportunity for a pragmatic trial comparing approved drugs that are the recommended first choice treatment in daily practice but have not been directly compared to each other. Given the above-mentioned results of network meta-analysis and retrospective cohort studies, the primary aim of such trials should include investigation of potential differences in bleeding risk. As such, we want to introduce the ongoing COmparison of Bleeding Risk between Rivaroxaban and Apixaban for the treatment of acute venous thromboembolism (COBRRA) study (ClinicalTrials.gov identifier: NCT03266783). The COBRRA study is a pragmatic, multicenter, prospective, randomized, open label, blinded end-point, superiority trial comparing bleeding outcomes between apixaban and rivaroxaban for treatment of acute VTE. Adult patients with acute objectively confirmed symptomatic VTE, defined as pulmonary embolism and/or proximal lower limb deep vein thrombosis, are eligible. To reflect patients seen in clinical practice, there are only a few exclusion criteria in contrast to original phase III trials, including anticoagulant treatment over 72 h prior to randomization or a contraindication to the use of apixaban or rivaroxaban as determined by the treating physician. Rivaroxaban and apixaban have been chosen as study drugs for this head-to-head trial for several reasons: 1) rivaroxaban and apixaban are the most frequently used DOACs; 2) they are the only DOACs that do not require a low-molecular-weight heparin lead-in period; 3) dabigatran has been associated with increased risk of myocardial infarction [21,42]; and 4) edoxaban is not reimbursed in most Canadian provinces. The primary outcome of the COBRRA study is clinically relevant bleeding, defined as major bleeding and clinically relevant non-major bleeding as per International Society on Thrombosis and Haemostasis definition [43,44]. The study aims to include and follow 2760 patients meeting eligibility criteria.

Many features of the COBRRA study are very pragmatic. Patients are recruited and treated by physicians in pre-existing settings for VTE treatment at participating centers of the CanVECTOR (Canadian Venous Thromboembolism Clinical Trials and Outcomes Research) network. The dosing of apixaban and rivaroxaban is based on approved dosages for acute VTE. Prescription and delivery of the medication is in accordance with local practice. Except for randomization, the provision of informed consent and assessment of quality of life, the study does not interfere with standard care including health care delivery, flexibility regarding co-interventions and follow-up. As such, the COBRRA trial is predestined to inform decisions regarding a daily clinical question relevant to patients, physicians and policymakers.

For extended treatment of VTE and for treatment of cancer-associated VTE, there are three head-to-head trials registered or ongoing. The hypothesis of the RENOVE (REduced Dose Versus Full-dose of Direct Oral Anticoagulant After uNprOvoked Venous thromboEmbolism) study is that a reduced dose of rivaroxaban or apixaban is non-inferior to a standard dose of rivaroxaban or apixaban in the reduction of recurrent VTE in patients at high risk of recurrence who completed 6 to 24 months of uninterrupted anticoagulation (ClinicalTrials.gov identifier: NCT03285438). The COVET (Comparison of Oral Anticoagulants for Extended VEnous Thromboembolism) study aims to evaluate whether apixaban and rivaroxaban are superior to warfarin in the reduction of clinically relevant bleeding during

Table 3
The nine PRECIS-2 domains for assessing the degree of pragmatism in a trial [40].

Eligibility	To what extent are the participants in the trial similar to those who would receive this intervention if it was part of usual care?
Recruitment	How much extra effort is made to recruit participants over and above what would be used in the usual care setting to engage with patients?
Setting	How different are the settings of the trial from the usual care setting?
Organisation	How different are the resources, provider expertise, and the organisation of care delivery in the intervention arm of the trial from those available in usual care?
Flexibility in delivery	How different is the flexibility in how the intervention is delivered and the flexibility anticipated in usual care?
Flexibility in adherence	How different is the flexibility in how participants are monitored and encouraged to adhere to the intervention from the flexibility anticipated in usual care?
Follow-up	How different is the intensity of measurement and follow-up of participants in the trial from the typical follow-up in usual care?
Primary outcome	To what extent is the trial's primary outcome directly relevant to participants?
Primary analysis	To what extent are all data included in the analysis of the primary outcome?

Score each domain using a 5-point Likert scale: 1, very exploratory; 2, rather exploratory; 3, equally pragmatic and exploratory; 4, rather pragmatic; 5, very pragmatic.

extended treatment for VTE in non-cancer patients (ClinicalTrials.gov identifier: NCT03196349). The CANVAS trial (Direct Oral Anticoagulants (DOACs) Versus LMWH ± Warfarin for VTE in Cancer: A Randomized Effectiveness Trial) is designed to assess whether direct oral anticoagulants are non-inferior to low-molecular weight heparins alone or with warfarin for treatment of acute cancer-associated VTE (ClinicalTrials.gov identifier: NCT02744092). Both COVET and CANVAS are sponsored by the Patient-Centered Outcomes Research Institute and similar to the COBRRA study, they have only few eligibility criteria to enhance generalizability of the results. All three, the RENOVE, COVET and CANVAS are prospective randomized open label blinded end-point trials. However, the COBBRA study is the only trial designed and powered to assess superiority of one DOAC over another and accordingly, the comparison between DOACs will only be of exploratory nature in the RENOVE, COVET and CANVAS studies.

5. Conclusion

Retrospective cohorts and indirect comparisons indicate that apixaban for treatment of acute VTE in non-cancer patients may be associated with the lowest risk of bleeding compared with other DOACs. The lack of direct comparison RCTs however, precludes definite judgment on superiority of apixaban. Head-to-head trials with DOACs are needed, because proper randomization including concealed treatment allocation remains the only way to effectively minimize selection bias and confounding for such comparisons. The fact that dabigatran, rivaroxaban, apixaban and edoxaban have been approved and are now recommended for both pulmonary embolism and deep vein thrombosis treatment presents an opportunity for pragmatic trials with minimal interference with standard care other than effective randomization. The COBRRA trial aims to evaluate whether apixaban is superior to rivaroxaban in the reduction of clinically relevant bleeding in non-cancer patients with acute symptomatic VTE. Designed as a pragmatic RCT, we expect that results of this study will provide health care users and physicians with answers to an important clinical question in daily practice.

Declaration of Competing Interest

T. Tritschler reports having received travel and congress fees from Pfizer.

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