The diagnostic and therapeutic management of pulmonary embolism

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CHAPTER 7

Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis

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ABSTRACT

Introduction

New direct oral anticoagulants (NOAC) constitute a novel treatment option for acute venous thromboembolism (VTE), with practical advantages. Individual studies have demonstrated comparable efficacy to that of vitamin K antagonists (VKA) and have suggested a more favorable safety profile. We performed a meta-analysis to determine the efficacy and safety of NOAC as compared with those of VKA in patients with acute VTE.

Methods

We searched MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews and the Clinical Trials Registry up to October 2013. Eligible studies included phase 3 trials comparing NOAC with VKA in patients with acute VTE. Relative risks (RR), absolute risk differences and numbers needed to treat (NNT) to prevent one event were calculated for recurrent VTE, fatal pulmonary embolism (PE), overall mortality, major bleeding, and other bleeding complications, with random-effects models.

Results

Five studies were included, investigating four NOAC (rivaroxaban, dabigatran, apixaban, and edoxaban) in 24 455 patients with acute VTE. RR for recurrent VTE, fatal PE and overall mortality for NOAC vs. VKA were 0.88 (95% confidence interval [CI] 0.74–1.05), 1.02 (95% CI 0.39– 5.96), and 0.97 (95% CI 0.83–1.14), respectively. The RR for major bleeding was 0.60 (95% CI 0.41–0.88). The NNT with NOAC instead of VKA to prevent one major bleed was 149. The RR and NNT for fatal bleeding were 0.36 (95% CI 0.15–0.87) and 1111. A fixed-effect network analysis did not demonstrate significant differences between individual NOAC and rivaroxaban.

Conclusions

NOAC have comparable efficacy to that of VKA, and are associated with a significantly lower risk of bleeding complications, although the NNT to prevent one major bleed was relatively high.

INTRODUCTION

Vitamin K antagonists (VKA) constitute the standard treatment for venous thromboembolism (VTE), which includes acute pulmonary embolism (PE) and deep vein thrombosis (DVT). VKAs are highly effective for the prevention of recurrent VTE, with a relative risk (RR) reduction of ~ 85% as compared with placebo, resulting in a recurrence risk of ~ 3% while patients are on treatment [1]. Two important limitations of VKA treatment are the need for tailored dosing based on frequent International Normalized Ratio monitoring, and the rate of major bleeding complications of ~ 2.1% during the first 6 months of treatment, with a case-fatality rate of 11% [2]. Intracranial bleeding account for 8.7% of major bleeds, and is associated with a mortality risk of ~ 46% [3]. Most major bleeds occur during the first weeks of VKA treatment, presumably because of an underlying bleeding predisposition [3,4].

In recent years, new direct oral anticoagulants (NOAC) have been developed, including factor IIa (thrombin) and FXa inhibitors, which lack some of the limitations of VKA treatment. The relatively stable pharmacokinetics and pharmacodynamics of these agents obviate the need for routine laboratory monitoring [5]. Several trials in patients with acute VTE have demonstrated comparable efficacy to that of VKA in terms of VTE recurrence rates, with lower risks of bleeding complications [6–10]. Nonetheless, the absolute risk of bleeding was low, ranging from 0.6% for fatal bleeding to 10.6% for a first major or clinically relevant non-major bleeding, most differences being non-significant. However, detailed knowledge about bleeding complications is imperative for the use of NOAC in patients with acute VTE. We therefore performed a systematic review and meta-analysis to assess the risks of recurrent VTE and bleeding complications in patients with acute VTE during treatment with NOAC as compared with VKA.

METHODS

Data sources and searches

We searched MEDLINE (via PubMed), EMBASE, the Cochrane Database of Systematic Reviews and the Clinical Trials Registry for peer-reviewed publications comparing NOAC with standard VKA treatment from inception to 25 October 2013. Our strategy included the National Library of Medicine's Medical Subject Headings keyword nomenclature and text words for VTE and NOAC, and validated search terms for randomized controlled trials. The complete search string is detailed in Data S1 (all supplementary files are available at http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1538-7836/). The electronic search was complemented with a manual review of reference lists of included articles and review articles. For unreported data, we additionally searched the authorization

documents available through the European Medicines Agency (www.ema.europa.eu/ema), and requested the manufacturer to provide unreported data.

Study selection and quality assessment

Search results were combined and duplicates were removed. Studies were screened for relevance by two independent reviewers, on the basis of title and abstract (T.vdH. and P.L.dE.). Discrepancies were resolved by consensus or by contacting a third reviewer (F.A.K.). Fulltext articles identified by either reviewer as potentially relevant were retrieved for further evaluation by the two reviewers. Inclusion criteria for eligible studies were as follows: (i) a phase 3 randomized controlled trial in patients with acute VTE comparing an orally administered direct FIIa inhibitor (including but not limited to dabigatran) or a direct FXa inhibitor (including but not limited to edoxaban, rivaroxaban, and apixaban) with VKA treatment; (ii) concerning a population with objectively diagnosed acute DVT, PE, or both; (iii) randomly allocating patients to the intervention groups; (iv) reporting outcomes after at least 3 months of follow-up, including the diagnosis of acute recurrent VTE based on predefined objective criteria in accordance with current international standards [11] and the rate of both major and clinically relevant non-major bleeding events, and adjudication of outcomes by an independent adjudication committee; and (v) publication in a peer-reviewed journal. Exclusion criteria were as follows: (i) studies concerning ximelagatran, as its use was rejected by the Food and Drug Administration, owing to concerns about potential liver toxicity; and (ii) studies evaluating extended anticoagulant treatment, as a proportion of patients in these studies were also included in the acute-phase studies, and we were only interested in patients with acute VTE, as most bleeding complications occur shortly after the initiation of anticoagulant treatment [3,4].

Risk of bias was evaluated in accordance with the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [12]. This tool evaluates the presence of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other risks of confounding.

Study outcomes and definitions

Efficacy outcomes were recurrent VTE, fatal PE, and overall mortality. Safety outcomes were major bleeding, non-fatal major bleeding at a critical site, clinically relevant non-major bleeding, non-fatal intracranial bleeding, major gastrointestinal bleeding, and fatal bleeding during anticoagulant treatment.

Recurrent symptomatic VTE included fatal and non-fatal PE and DVT. Recurrent VTE was considered as a cause of death if there was objective documentation in terms of

autopsy, or if death could not be attributed to another documented cause of death and PE could not be ruled out.

The definition of major bleeding was similar for all included studies: overt and associated with a decrease in the hemoglobin level of ≥ 2 g/dL, requiring transfusion of at least two units of blood, occurring in a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular intramuscular with compartment syndrome, retroperitoneal), or contributing to death [13]. In all included studies, except for the Re-Cover study, clinically relevant non-major bleeding was defined as overt bleeding not meeting the criteria for major bleeding complications, but associated with medical intervention, contact with a physician, interruption of study drug, or discomfort or impairment in carrying out activities in daily life [14]. In the Re-Cover study, several criteria were established for clinically relevant non-major bleeding that are comparable with the definition used in the other trials.

Data extraction

Data extraction was independently performed by two reviewers. For each included study, we extracted the number of participants, follow-up period, number of patients with DVT, PE, or both, unprovoked VTE, active malignancy, previous VTE, and the mean time spent in therapeutic range (TTR) during VKA therapy.

Data synthesis and analysis

Data were analyzed with the Mantel–Haenszel random-effects model, by the use of Review Manager (V. 5.1; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen). RRs with corresponding 95% confidence intervals (CI) were reported. Comparisons were performed for all endpoints. Statistical heterogeneity was assessed and quantified with the Cochrane Q-test and the I^2-statistic, respectively. Absolute risk differences with CI and the number needed to treat (NNT) with NOAC in order to prevent one outcome event were calculated. The NNT calculation was based on the point estimate of the absolute risk difference. The presence of publication bias was evaluated with funnel plots, with formal tests for funnel plot asymmetry being used only in the case of inclusion of at least 10 studies.

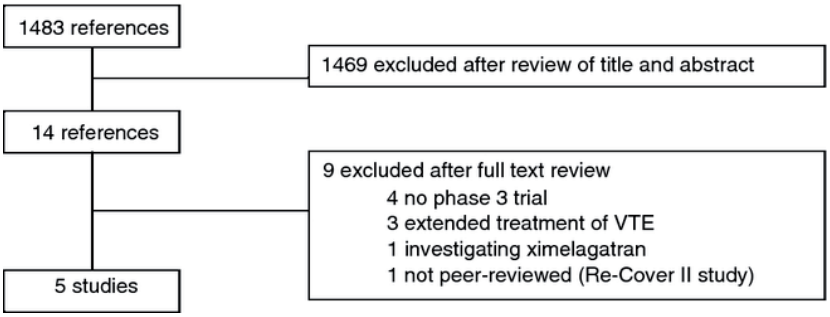
In the absence of trials making direct comparisons between NOAC, we performed a fixed-effect network analysis based on inverse variance weighting. In this analysis, dabigatran, apixaban and edoxaban were compared with rivaroxaban. Rivaroxaban was chosen as the comparator, as this is the only drug currently registered for the treatment of acute VTE.

RESULTS

Study selection

The initial search identified 889 records in PubMed, 453 unique records in EMBASE, 67 unique records in the Cochrane Database of Systematic Reviews, and 74 records from the Clinical Trials Registry, resulting in a total of 1483 references. On the basis of screening of titles and abstracts, 14 studies were selected for full text review. Of these 14 studies, four were excluded because they were not phase 3 trials [12,15–17], the Re-Cover II study was excluded because this study had not yet been published in a peer-reviewed journal [18], the THRIVE II/V study was excluded because of the use of ximelagatran (application rejected by the Food and Drug Administration because of concerns about potential liver toxicity) [19], and three references were excluded because extended treatment of VTE was investigated [20–22]. Therefore, five studies were eligible for inclusion (**Figure 1**) [6–10].

Figure 1. Flow diagram of study selection.



Note: VTE, venous thromboembolism.

Characteristics of included randomized controlled trials

One study evaluated dabigatran in patients with PE and/ or DVT (Re-Cover I study) [6], one investigated rivaroxaban in patients with DVT (Einstein-DVT study) [7], one investigated rivaroxaban in patients with PE (Einstein-PE study) [8], one investigated apixaban in patients with DVT and/or PE (Amplify study) [9], and one investigated edoxaban in patients DVT and/or PE (Hokusai study) [10]. In total, 24 455 patients were included, of whom 57% were male. The mean age ranged between 55 and 58 years. The percentage of patients with unprovoked VTE varied from 62% to 90%. Overall, PE was present in 10 796 patients (44%), and 13 607 (56%) had isolated proximal DVT. Active malignancy was present in 1465 patients (6%), 4651 patients (19%) had experienced a previous VTE, and the TTR ranged from 58% to 64% (**Table 1**). Dabigatran (150 mg twice daily) and edoxaban (60 mg once daily, or 30 mg once daily in the case of a creatinine clearance of 30–50 mL/min or a body weight of < 60 kg) were combined with weight-adjusted therapeutic-dose low molecular weight heparin or unfractionated heparin as initial

Table 1. Study characteristics.

Study Year Drug Class	Treatment duration in months	Patients n	Men n (%)	Mean age in years	PE or PE and DVT n (%)	Isolated DVT n (%)	Unprovoked n (%)	Cancer n (%)	Previous VTE n (%)	TTR in VKA group %
Re-Cover 2009 Dabigatran DTI	6	2539	1484 (58)	55	786 (31)	1749 (69)	Not provided	121 (5)	649 (26)	60
Einstein-DVT 2010 Rivaroxaban FXa inhibitor	3/6/12*	3449	1960 (57)	56	23 (1)	3405 (99)	2138 (62)	207 (6)	666 (19)	58
Einstein-PE 2012 Rivaroxaban FXa inhibitor	3/6/12*	4832	2556 (53)	58	4832 (100)	0 (0)	3117 (65)	223 (5)	944 (20)	63
Amplify 2013 Apixaban FXa inhibitor	6	5395	3167 (59)	57	1836 (34)	3532 (65)	4845 (90)	143 (3)	872 (16)	61
Hokusai 2013 Edoxaban FXa inhibitor	3/6/12*	8240	4716 (57)	56	3319 (40)	4921 (60)	5410 (66)	771 (9)	1520 (18)	64

* Treatment duration defined by treating physician.

Note: DTI: direct thrombin inhibitor; Fxa inhibitor: factor Xa inhibitor; PE: pulmonary embolism; DVT: deep vein thrombosis; VTE: venous thromboembolism; TTR: time in therapeutic range; VKA: vitamin K-antagonists.

treatment for at least 5 days, whereas rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) and apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily) were used as single-drug regimens. In the Re-Cover study and the Amplify study, patients were treated for 6 months; in the Einstein studies and the Hokusai study, the treating physician determined the treatment duration. In the Einstein-DVT study, 63% of the patients were treated for 6 months, 25% for 12 months, and 12% for 3 months. In the Einstein-PE study, 57% of the patients were treated for 6 months, 37% for 12 months, and 5% for 3 months. In the Hokusai study, 12% of the patients were treated for 3 months, 26% for 3–6 months, and 61% for > 6 months.

All included studies were of good quality as determined by the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (**Figure 2**). Most important potential risks of bias were associated with the open label design of the two Einstein studies [7,8], and all five studies were sponsored and managed by the pharmaceutical industry. As our meta-analysis included only five studies, we did not perform formal tests for funnel plot asymmetry (Data S2).

Figure 2. Results of Cochrane Collaboration's tool for assessing risk of bias.

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Re-Cover 2009	+	+	+	+	+	+	-
Einstein-DVT 2010	+	+	-	+	+	+	-
Einstein-PE 2012	+	+	-	+	+	+	-
Amplify 2013	+	+	+	+	+	+	-
Hokusai 2013	+	+	+	+	+	+	-

Note: key: +: Low risk of bias; -: High risk of bias.

Meta-analysis: efficacy outcomes

During anticoagulant treatment, recurrent VTE occurred in 241 of the 12 151 patients (2.0%) treated with NOAC and in 273 of the 12 153 patients (2.2%) treated with VKA. In accordance with the results of the individual studies, the combined RR for recurrent VTE did not demonstrate a significant difference between these drug classes: 0.88 (95% CI 0.74–1.05) (**Table 2; Figure 3**). Fatal PE occurred in nine of the 12 151 patients (0.07%) treated with NOAC and in nine of the 12 153 patients (0.07%) treated with VKA. In total, 290 of the 12 197 patients (2.4%) treated with NOAC and 298 of the 12 193 patients (2.4%) treated with VKA died during follow-up. The RR for all-cause mortality was 0.97 (95% CI 0.83–1.14). The I^2 of all evaluated efficacy outcomes was 0%, indicating low heterogeneity.

Table 2. Efficacy and safety outcomes.

Outcome	NOAC n % Range	VKA n % Range	Pooled absolute risk difference % 95% CI	NNT with NOACs to prevent 1 event
Recurrent VTE	241/12,151 2.0 1.6-2.4	273/12,153 2.2 1.8-3.0	-0.24 -0.060 to 0.11	417
Fatal PE	9/12,151 0.07 0.04-0.10	9/12,153 0.07 0.00-0.24	0.01 -0.06 to 0.08	10,000
Overall mortality	290/12,197 2.4 1.5-3.2	298/12,193 2.4 1.7-3.1	-0.10 -0.47 to 0.28	1,000
Major bleeding	131/12,197 1.1 0.6-1.6	211/12,193 1.7 1.2-2.2	-0.67 -1.13 to -0.21	149
Non-fatal bleeding at a critical site	28/12,179 0.23 0.08-0.32	77/12,193 0.63 0.18-1.08	-0.38 -0.65 to -0.10	263
Clinically relevant non-major bleeding	806/12,179 6.6 3.9-9.5	1024/12,193 8.4 6.9-9.8	-1.77 -3.40 to -0.15	56
Non-fatal intracranial bleeding	11/12,179 0.09 0.00-0.12	31/12,193 0.25 0.00-0.42	-0.14 -0.31 to 0.03	714
Major gastrointestinal bleeding	28/8,079 0.35 0.17-0.71	43/8,071 0.53 0.23-0.67	-0.16 -0.42 to 0.11	625
Fatal bleeding	7/12,179 0.06 0.04-0.08	21/12,193 0.17 0.07-0.29	-0.09 -0.17 to 0.00	1,111

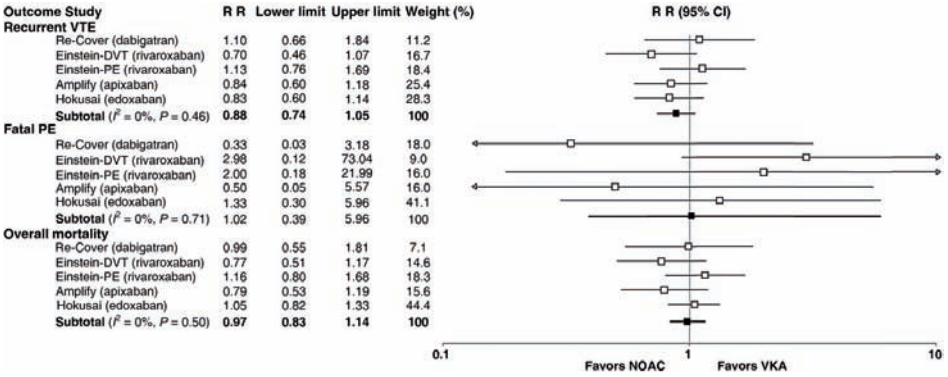
Note: NOAC: new direct oral anticoagulants; VKA: vitamin K-antagonists; NNT: number needed to treat; CI: confidence interval; VTE: venous thromboembolism; PE: pulmonary embolism.

Meta-analysis: safety outcomes

All combined RR were significantly lower for the patients treated with NOAC, except that for major gastrointestinal bleeding (**Table 2; Figure 4**). Major bleeding occurred in 1.1% of the patients treated with NOAC and in 1.7% of the patients treated with VKA, with an accompanying combined RR of 0.60 (95% CI 0.41–0.88) and an I^2 of 62%. The combined absolute risk difference for major bleeding was -0.67% (95% CI -1.13 to -0.21), resulting in an NNT with NOAC instead of VKA of 149 (95% CI 88–476).

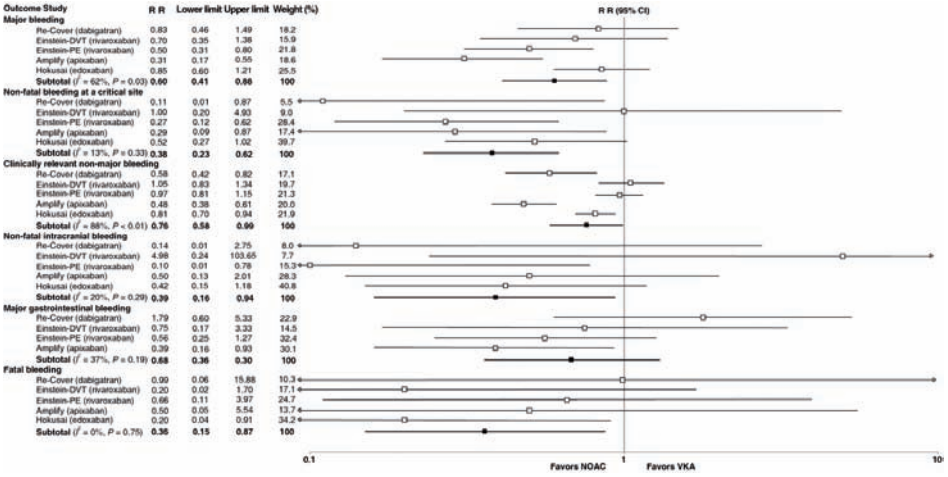
Non-fatal bleeding at a critical site occurred in 0.23% of the patients treated with NOAC and in 0.63% of the patients treated with VKA. The combined RR was 0.38 (I^2 = 13%; 95% CI 0.23–0.62) and the absolute risk difference was -0.38% (95% CI -0.65 to -0.10), resulting in an NNT of 263 (95% CI 153–1000).

Figure 3. Efficacy outcomes.



Note: NOAC: New Direct Oral anticoagulants; VKA: vitamin-K antagonists.

Figure 4. Safety outcomes.



Note: NOAC: New Direct Oral anticoagulants; VKA: vitamin-K antagonists.

The combined RR for clinically relevant non-major bleeding was 0.76 (95% CI 0.58–0.99). This risk varied considerably between the individual studies (I^2 of 88%). In the studies investigating rivaroxaban (Einstein-DVT and Einstein-PE), the RR were very similar, whereas in the studies investigating dabigatran, apixaban, and edoxaban, the RR were in favor of NOAC.

Non-fatal intracranial bleeding occurred in 0.09% of the patients treated with NOAC- and in 0.25% of the patients treated with VKA, resulting in a combined RR of 0.39 (95% CI 0.16–0.94). Only in the Einstein-DVT study was the incidence higher in patients treated with rivaroxaban than in those treated with VKA: two events in 1718 patients vs. 0 in 1711 patients. In the EINSTEIN-PE study, which also evaluated rivaroxaban, the opposite

association was observed. Owing to the low incidence rates of intracranial bleeding and the wide CI, the I^2 was only 20%.

The incidence of major gastrointestinal bleeding was not reported in the Hokusai study, and the combined RR of the other four studies for NOAC was 0.68 (I^2 = 37%; 95% CI 0.36–1.30); only the Re-Cover study, the only study that investigated a direct thrombin inhibitor (dabigatran), reported a higher risk. In this study, the incidence rates were 0.71% (9/1273) in patients treated with dabigatran and 0.39% (5/1266) in patients treated with VKA, a difference of 0.31% (95% CI -0.26 to 0.89).

Fatal bleeding occurred in seven of the 12 179 patients (0.06%) treated with NOACand in 21 of the 12 193 patients (0.17%) treated with VKA, with a combined RR of 0.36 (95% CI 0.15–0.87) and an NNT of 1111 (95% CI 588–0). All studies demonstrated RR in favor of NOAC, with wide CI because of the low incidence rates, resulting in an I^2 of 0%.

Fixed-effect network analysis

In a fixed-network analysis, dabigatran, apixaban and edoxaban were compared with rivaroxaban for the predefined efficacy and safety endpoints. No statistically significant differences were observed for all outcomes. For recurrent VTE, P-values ranged from 0.74 to 0.85, and for major bleeding they ranged from 0.48 to 0.60. The results of the other evaluated outcomes are provided in Data S3.

DISCUSSION

For all of the evaluated efficacy outcomes, the pooled RR were comparable between patients treated with NOAC and patients treated with VKA. In contrast, statistically significantly lower risks were observed for all evaluated bleeding complications during treatment with NOAC than during treatment with VKA, except for the risk of major gastrointestinal bleeding. This is probably attributable to a lack of power, as the Hokusai study did not report major gastrointestinal bleeding separately, and therefore could not be included in this specific analysis. We asked for this information from the manufacturer in vain.

Despite the lower bleeding risk with the new agents, our analyses indicate that the advantage of NOAC in absolute terms is somewhat limited for patients with acute VTE who need anticoagulant treatment for a relatively short duration. This is reflected by the high NNT for treatment with NOAC instead of VKA, ranging from 56 to prevent a clinically relevant non-major bleeding to even 1111 to prevent one fatal bleeding. Although the inclusion criteria of the trials ruled out patients with any bleeding risks, the relatively high NNT cannot be explained by an overall low incidence of bleeding, as the bleeding incidences from the pooled studies are very similar to those of other large VTE treat-

ment studies [3]. Therefore, when NOAC are introduced as a generally accepted therapy for acute VTE, the relatively small net benefit should be weighed against the financial consequences of using this costly drug class.

Last year, the first meta-analysis of the efficacy and safety of NOAC for the treatment of acute VTE was published, with partly overlapping patient cohorts [23]. The major difference between that meta-analysis and our study is the inclusion of relatively small phase 2 trials with shorter durations of follow-up and different NOAC dosages, and studies on ximelagatran by Fox et al [12,19]. By including the recently published trials on apixaban and edoxaban, we exceed their sample size while restricting our analysis to robust data of high quality.

Regarding the extended treatment of VTE, i.e. beyond the treatment during the first 3–6 months, the efficacy and safety of NOAC as compared with VKA are still unclear. In only one study was dabigatran randomly compared with VKA during extended treatment; hazard ratios for recurrent VTE of 1.44 (95% CI 0.78–2.64) and 0.54 (95% CI 0.41–0.71) for major or clinically relevant non-major bleeding were reported [21]. In two other studies, apixaban and rivaroxaban were randomly compared with placebo and were included in a recently published meta-analysis [24]. As expected, these drugs showed high efficacy as compared with placebo, but their efficacy and safety as compared with VKA remain to be demonstrated.

Given the absence of the possibility of direct comparisons between the individual NOAC, we performed an indirect comparison of dabigatran, apixaban and edoxaban with rivaroxaban. Although differences in efficacy and safety outcomes between individual drugs can be reasonably expected, no significant differences in efficacy and safety outcomes were observed. Owing to the relatively low incidence rates of all outcomes, large randomized controlled trials in > 20 000 patients would be required to identify potentially relevant differences between the NOAC. For practical reasons, it seems very unlikely that such studies will be initiated in the (near) future. Therefore, pooling the results of all separate studies evaluating different NOAC in comparison with VKA provides the best available evidence for deciding whether NOAC constitute a suitable alternative, or are even preferable, to VKA for the treatment of acute VTE.

Although not identified by the fixed-effect network analysis, reasonably expected differences between the individual drugs may be the reason for the high heterogeneity observed for major bleeding (I^2 = 62%) and clinically relevant non-major bleeding (I^2 = 88%).

Considering major bleeding, all studies demonstrated RR in favor of NOAC, but the effect size differed. For clinically relevant non-major bleeding, in particular, the RRreported in the Einstein studies differed from the other RR. This might be explained by a specific effect of rivaroxaban, or it could be a result of the PROBE design of the Einstein studies, as the other studies were double-blind studies. For major gastrointestinal bleeding, the

relatively high heterogeneity ($I^2 = 37\%$) seems to be explained by the higher RR reported in the Re-Cover study. This might be explained by an individual drug effect or a difference between drug classes (FIIa inhibitors and FXa inhibitors).

The more favorable safety profile of NOAC may be ascribed to their more stable anticoagulant effect than that of VKA [5]. The lower risk of intracranial bleeding may be a consequence of maintaining normal concentrations of FVII and the formation of FVIIa–tissue factor complexes, which play an important role in cerebral vascular damage [25]. Other supposed mechanisms are the reduced suppression of thrombin at the site of cerebral injury, and the inability of rivaroxaban to substantially penetrate the blood–brain barrier [26].

A concern regarding NOAC is the absence of specific antidotes. On the basis of experimental studies, non-specific prohemostatic agents are recommended for direct reversal of the anticoagulant effect [27,28]. It is of note that patients with a major bleed while on dabigatran had a better prognosis than patients with a major bleed while on VKA[29]. Furthermore, the lower bleeding risk and the presumed introduction of specific antidotes in the coming years put this concern in perspective.

Our study has limitations. First, because of the absence of studies comparing the same drugs, we were unable to perform a random-effects Bayesian network meta-analysis. Even so, the alternatively performed fixed-effect network analysis did not demonstrate significant differences between the individual drugs. Second, we were unable to perform subgroup analyses for patients with PE and DVT. Third, we could not differentiate between early and late bleeding occurrences, as detailed data were lacking. Fourth, treatment durations were not identical throughout the studies, although most patients were subjected to a 6-month anticoagulant course. Fifth, in the Hokusai study, the safety outcomes of fatal PE and overall mortality were only reported for the total follow-up duration. Sixth, the results of this meta-analysis should not be generalized to all patients with acute VTE, as specific populations, including the elderly, patients with cancer, patients with renal insufficiency, patients with rare localizations of VTE (e.g. distal DVT, splanchnic thrombosis, and cerebral vein thrombosis), and patients with morbid obesity, were underrepresented or excluded. Finally, two studies had a PROBE design, in which participants and researchers were aware of the treatment allocation, and only the adjudication committee was blinded. It has been suggested that the open design of PROBE studies leads to a more real-world study population, owing to the easier recruitment of patients, although the risk of reporting bias might be increased. Furthermore, this design may influence decisions regarding other medical treatments. Hence, it has been suggested that the PROBE design could result in overoptimistic results in favor of NOAC. Even so, recent studies evaluating NOAC in patients with atrial fibrillation or VTE have not demonstrated such an effect [30,31].

In conclusion, NOAC show comparable efficacy to VKA in patients with acute VTE, as well as greater practical simplicity and a more favorable bleeding profile, although the absolute benefit was somewhat limited, owing to the high NNT.

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