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Comparative efficacy and safety of anticoagulants and aspirin for extended treatment of

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Abstract (305 words)

Objective: To systematically review the literature and to quantitatively evaluate the efficacy and safety of extended pharmacologic treatment of venous thromboembolism (VTE) through network meta-analysis (NMA).

Methods: A systematic literature search (MEDLINE, Embase, Cochrane CENTRAL, through September 2014) and searching of reference lists of included studies and relevant reviews was conducted to identify randomized controlled trials of patients who completed initial anticoagulant treatment for VTE and then randomized for the extension study; compared extension of anticoagulant treatment to placebo or active control; and reported at least one outcome of interest (VTE or a composite of major bleeding or clinically relevant non-major bleeding). A random-effects Frequentist approach to NMA was used to calculate relative risks with 95% confidence intervals.

Results: Ten trials (n=11,079) were included. Risk of bias (assessed with the Cochrane tool) was low in most domains assessed across the included trials. Apixaban (2.5mg and 5mg), dabigatran, rivaroxaban, idraparinux and vitamin K antagonists (VKA) each significantly reduced the risk of VTE recurrence compared to placebo, ranging from a 73% reduction with idraparinux to 86% with VKAs. With exception of idraparinux, all active therapies significantly reduced VTE recurrence risk versus aspirin, ranging from a 73% reduction with either apixaban 2.5mg or rivaroxaban to 80% with VKAs. Apixaban and aspirin were the only therapies that did not increase composite bleeding risk significantly compared to placebo. All active therapies except aspirin increased risk of composite bleeding by 2 to 4-fold compared to apixaban 2.5mg, with no difference found between the two apixaban doses.

Conclusion: Extended treatment of VTE is a reasonable approach to provide continued protection from VTE recurrence although bleeding risk is variable across therapeutic options. Our results indicate that apixaban, dabigatran, rivaroxaban, idraparinux and VKAs all reduced VTE recurrence when compared to placebo. Apixaban appears to have a more favorable safety profile compared to other therapies.

Introduction

Over 1.8 adults per 1000 develop acute venous thromboembolism (VTE) annually.[1] International guidelines recommend initial parenteral anticoagulation plus an oral vitamin-K antagonist (VKA) for >3 months.[1] While highly effective in reducing the risk of deep-vein thrombosis (DVT) and pulmonary embolism (PE) recurrence during therapy, there is considerable risk after treatment is stopped. One and five-year VTE recurrence risk is estimated to be 1-5% and 3-15% in patients with provoked VTE and 10% and 30% in those with unprovoked VTE.[1,2] This ongoing risk raises the question as to the appropriate duration of anticoagulant therapy and whether extending treatment beyond the acute period would improve patient outcomes. Extended anticoagulant therapy also comes with risks, primarily that of bleeding that must be weighed against the possible benefits. Several randomized controlled trials (RCTs) have evaluated the practice of extended anticoagulation for the treatment of VTE. We aimed to systematically review the literature and to quantitatively evaluate the efficacy and safety of extended pharmacologic treatment of venous thromboembolism (VTE) through network meta-analysis (NMA).

Methods

We conducted a systematic literature search in MEDLINE (via Ovid), Embase and Cochrane Central databases from the earliest possible search date through September 2014. The search strategy for MEDLINE is presented in Appendix A and a similar strategy was used for the other databases. A manual search was also performed using the references of clinical trials and review articles to identify additional relevant articles. Results of identified studies were supplemented when possible by contacting investigators for clarification or additional data. For

a study to be included in the analysis, it had to: 1) be an RCT evaluating patients who completed initial anticoagulant treatment for either a DVT, PE or both prior to randomization for the extension study; 2) compare extension of VTE treatment with an anticoagulant or antiplatelet to placebo or active control; and 3) report at least one outcome of interest [e.g., recurrent VTE (DVT and/or PE) or the composite of major bleeding or clinically relevant non-major bleeding (CRNMB)]. We also evaluated the individual components of these composite outcomes separately (DVT, nonfatal PE, fatal PE, major bleeding, CRNMB and all-cause mortality).

Two independent investigators separately reviewed all citations identified by the search for inclusion (title and abstract stage, full text stage) and abstracted data from included trials. Disagreements were resolved through discussion. The following data were collected from each trial: author identification, year of publication, funding source, report of conflicts of interest, study design characteristics, study population (inclusion and exclusion criteria, geographic location, length of study, duration of patient follow-up), patient baseline characteristics, VTE treatment regimen (name, strength, frequency, dose, route of administration, duration of therapy, time in therapeutic range for VKA arms), and outcomes data (number of events, definitions, period of follow-up, and diagnostic tests for confirmation).

To assess the methodological quality of the included trials, the Cochrane Collaboration risk of bias tool was used.[3] This tool evaluates seven domains including sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and any other identifiable biases. Each individual domain is assessed as having low, high, or unclear risk of bias using the

guidance provided by the tool. The risk of bias was evaluated for each trial by two separate

investigators and conflicts were resolved through discussion.

We first ran traditional pairwise meta-analysis on the primary outcomes of interest,

when more than one trial comparing the same interventions was available. A random-effects

model was used to calculate relative risks (RR) and pool baseline event rates, each with

corresponding 95% confidence intervals (CIs). A p-value of <0.05 was considered statistically

significant for all analyses. Statistical heterogeneity was addressed using the I^2 statistic, with

values of 25%, 50% and 75% representing cut-off values for low, moderate and high likelihood

of the presence of heterogeneity.[4] StatsDirect version 2.8.0 was used for these analyses.

In addition to traditional meta-analyses, NMA was performed.[5] NMA is a generalization

of traditional pairwise meta-analysis that compares all pairs of treatments within a set of

treatments for the same disease state. Along with analyzing the direct within-trial comparisons

between 2 treatments (such as VKAs vs. placebo), the NMA framework enables incorporation of

indirect comparisons constructed from 2 trials that have 1 treatment in common, such

dabigatran vs. placebo and VKAs vs. placebo, allowing the indirect comparison of dabigatran

with VKAs through the common comparator of placebo.[5] This type of analysis safeguards the

within-trial randomized treatment comparison of each trial while combining all available

comparisons between treatments. We used the package 'netmeta' (version 0.5-0) in R (version

3.0.2, The R Foundation for Statistical Computing) to perform NMA.[6] The package uses a novel

graph-theory methodology that exploits the analogy between treatment networks and

electrical networks to construct a NMA model accounting for the correlated treatment effects

in multi-arm trials. This approach has been found to be equivalent to the Frequentist approach

to NMA.[7] We implemented a random-effects model assuming common heterogeneity across all

comparisons. In order to assess for the presence of whole network heterogeneity as well as

inconsistency in our NMA, we utilized generalized Cochran Q statistics for multivariate meta-

analysis as described by Krahn and colleagues.[8] We did not include two trials[9,10] in the base-

case analyses because the enrolled populations were unique in comparison to the remaining

trials. AUREC-FVII trial enrolled patients with elevated factor 7 levels at baseline while Vitovec

et al. enrolled patients with residual vein thrombosis at baseline. None of the other trials

focused in on such a specific population which could have led to differing baseline risk of VTE.

Instead, we performed a sensitivity analysis on the primary outcomes by adding these two trials

into the base-case analysis.

Results

Study selection and characteristics

The results of our literature search are presented in Figure 1. After duplicates were

removed, 928 citations were screened for inclusion. Of those, 890 and 27 citations were

excluded at the abstract and full text level, respectively, leaving 11 citations reporting 12

unique trials[9-19] (Table 1). Rivaroxaban[12] and idraparinux[16] were each evaluated in comparison

to placebo in individual trials (Figure 2). Two doses of apixaban (2.5mg and 5mg twice daily)

were compared to placebo in one trial[11], and each dose was considered separately in our

analysis (as a three arm trial). Dabigatran was compared to placebo in one trial and to warfarin

in a second trial, both published within the same report.[13] VKAs were compared to either

placebo or control (i.e., discontinuation of VKA therapy with no placebo administration) in five

trials.[9,10,17-19] Finally, aspirin was compared to placebo in two trials.[14,15] Six trials were judged to

have low risk of bias in all domains evaluated (appendix Figure 1).[11-15] Two trials had low risk of

bias in all domains except the blinding of outcomes assessment in which the risk of bias was

unclear.[16,19] The remaining four trials, which all evaluated the active intervention of VKA, had

unclear randomization procedures.[9,10,17,18] Three of these trials had high risk of bias because the

trials were not blinded to participants and personnel.[9,17,18]

The 10 trials in our base-case analysis represent a total of 11,079 patients.[11-19] With the

exception of one trial that enrolled exclusively patients with an index DVT, the index event was

PE in 22.7% to 49% of patients and DVT in 55.3% to 76% of patients. Four trials enrolled

patients with unprovoked index VTE exclusively and the remaining trials that reported this

characteristic had greater than 50% representation of unprovoked VTEs (range 55.9% to

93.2%). Extended treatment duration ranged across trials from an additional 6 months to up to

4 years after the initial VTE treatment was completed. Four trials that evaluated a VKA reported

time in therapeutic range, which ranged from 64% to 83%.

Traditional meta-analysis was performed on primary outcomes of interest [recurrent

VTE (DVT and/or PE) or the composite of major bleeding or clinically relevant non-major

bleeding (CRNMB)] and was possible for two of the seven active interventions in the network,

aspirin and VKAs, both compared to placebo. The remaining interventions were only

represented by one trial each. Aspirin decreased the risk of recurrent VTE significantly [RR 0.72

(0.56 to 0.93)] and did not significantly impact the risk of composite bleeding [RR 1.48 (0.71 to

3.06)] compared to placebo. VKAs did not significantly reduce the risk of recurrent VTE [RR 0.18

(0.03 to 1.08)]. We could not evaluate the composite bleeding outcome since this data was not

reported in trials evaluating VKAs and we were unable to evaluate heterogeneity as there were

only two trials pooled for each direct pairwise comparison. The pooled proportion of patients with recurrent VTE amongst placebo or untreated controls was 11% (7% to 15%) with an I^2 value of 93.5% suggesting a high-likelihood of heterogeneity (Appendix Figure 2). The pooled proportion of patients with major bleed and CRNMB amongst placebo or untreated controls was 1.9% (1.5% to 2.4%) with an I^2 value of 0% (Appendix Figure 3).

Nine trials were included in the network to evaluate recurrent VTE and all active therapies were represented.[11-17,19] According to results of the NMA, each individual active therapy decreased the risk of recurrent VTE significantly compared to placebo, with exception of aspirin which did not significantly impact this outcome (Figure 3). Each individual active therapy, with exception of idraparinux, significantly reduced recurrent VTE risk in comparison to aspirin. There were no other significant differences in recurrent VTE risk when comparing one active therapy to another. There were no strong signals of whole network heterogeneity (p=0.112) or inconsistency (p=0.08).

Upon analysis of individual outcomes comparing each active therapy relative to placebo, all therapies decreased DVT risk with exception of aspirin and idraparinux and all therapies decreased non-fatal PE risk with exception of aspirin and apixaban 2.5mg (Table 2). No significant findings were noted for the outcome of fatal PE and of the few therapies where PE could be evaluated, idraparinux significantly reduced risk versus placebo. Mortality risk was significantly decreased by apixaban 5mg compared to placebo [RR 0.29 (0.10 to 0.87)]. For each of these individual outcomes, there were no signs of network heterogeneity or inconsistency.

Seven trials were included in the network used to evaluate the composite bleeding outcome and all active therapies were represented.[11-16] When compared to placebo, all active

therapies increased composite bleeding risk except both apixaban doses and aspirin. VKAs significantly increased composite bleeding risk compared to all active therapies except idraparinux and rivaroxaban. Risk was also significantly increased with rivaroxaban compared to both doses of apixaban and aspirin. Idraparinux and dabigatran significantly increased composite bleeding risk in comparison to apixaban 2.5mg. There were no suggestions of whole network heterogeneity (p=0.468) or inconsistency (p=1.00). Evaluation of the individual components of the composite bleeding outcome indicate that major bleeding risk was increased with idraparinux [RR 23.81 (1.42 to 400.35)] and VKAs [RR 4.64 (1.31 to 16.41)] compared to placebo. CRNMB risk was increased with apixaban 5mg [RR 1.82 (1.05 to 3.15)] and rivaroxaban [RR 4.53 (2.03 to 10.11)] compared with placebo. There were no signs of network heterogeneity or inconsistency for either bleeding outcome.

When AUREC-FVII was added to the base case analysis of recurrent VTE (Vitovec et al. did not report recurrent VTE data), it did not impact the results of any therapy comparisons in terms of magnitude or direction of effect. Sensitivity analysis was not performed on the composite bleeding outcome since neither AUREC-FVII nor Vitovec et al. reported these data. Lastly, we conducted an exploratory post-hoc analysis of the new oral anticoagulants for the two primary outcomes of interest (Figure 4). None of the anticoagulants differed in recurrent VTE risk in comparison to each other, as was seen in our base-case analysis. Apixaban 2.5mg reduced the risk of composite bleeding compared to dabigatran while both apixaban doses each decreased composite bleeding risk compared to rivaroxaban, again consistent with our base-case analysis.

Discussion

The concept of extended anticoagulation for patients with VTE remains a topic of debate. Current guidelines from the American College of Chest Physicians support extended VTE treatment, defined as treatment beyond 3 months with no defined stop date, primarily in patients with unprovoked proximal DVT or PE with low to moderate bleeding risk.[1] Results of this NMA evaluating over 11,000 patients who completed acute VTE treatment provide additional justification for these recommendations. The model found that apixaban (either dose), dabigatran, rivaroxaban, idraparinux or VKAs reduced the risk of VTE recurrence compared to placebo without appreciable differences in efficacy between each therapy. Aspirin was not found to impact recurrent VTE risk significantly compared to placebo.

Of the active therapies which were significantly better than placebo in reducing VTE risk (apixaban 2.5mg, apixaban 5mg, dabigatran, rivaroxaban, idraparinux and VKAs), safety data suggests that dabigatran, rivaroxaban and VKAs each independently increased bleeding risk significantly compared with apixaban 2.5mg. There was no difference found when comparing the two studied apixaban doses. Post-hoc analysis of a model comprised of only the new oral anticoagulants supported this finding, suggesting that apixaban reduced the composite bleeding risk over dabigatran (apixaban 2.5mg dose) and rivaroxaban (both apixaban doses). An overall review of the efficacy and safety outcomes in this analysis suggests that apixaban may be the best choice for extended VTE treatment.

When evaluating individual components of the composite outcomes, efficacy was observed in the reduction of DVT and non-fatal PE risk. Limitations in the number of events and data reported for PE and fatal PE make interpretation of a lack of benefit in these outcomes less certain. Mortality was found to be significantly reduced with apixaban 5mg compared to

placebo while the 2.5mg dose of apixaban was trending in the same direction. However, given close to 200 statistical comparisons are presented, it is reasonable to expect 10 significant findings are in error. In addition, the number of deaths per treatment arm is small, lending more uncertainty to the results on mortality. Finally, most warfarin trials did not report CRNMB which limited the power to analyze this outcome independently from major bleeding.

The results of this NMA reflect a patient population supported by guidelines for extended anticoagulation: unprovoked VTE with low to moderate bleeding risk. The trials included in our NMA evaluated either exclusively a population of patients with first unprovoked VTE or a mixed population of predominantly unprovoked cases. Patients with provoked VTE or recurrent VTE were not extensively represented. Pooling the proportion of patients with recurrent VTE in placebo and untreated controls suggested statistically significant heterogeneity in baseline risk for this outcome. Three trials appeared to have higher baseline VTE risk relative to the others, including both aspirin trials (WARFASA and ASPIRE) and the trial evaluating warfarin by Kearon et al.[14,15,19] These were three of the four trials that enrolled exclusively unprovoked VTE cases and therefore it is not surprising that the baseline risk was elevated in comparison to trials allowing enrolment of patients with provoked VTE events. Another factor which may be contributing to the heterogeneity is the duration of treatment and follow-up, which was the longest for the aspirin trials at approximately 2 and 4 years. Naturally with longer duration of follow-up, more events are likely to accumulate in comparison to the remaining trials which had a follow-up period of 1 year or less.

There are additional factors clinicians should consider when evaluating the applicability of these results. Gender was well balanced across trials. Although extremes of adult age were

eligible for trial enrollment, based on the reported means and standard deviations, the majority of enrolled patients were aged 40 to 70 years. Not only does advanced age increase VTE risk, but this is also a known risk factor for bleeding. Patients with other characteristics that increase bleeding risk were commonly excluded from the trials and so together with the likely age distribution the results of this NMA reflect a patient population with a relatively low baseline risk of bleeding. This was also supported by the pooled proportion of major bleeding and CRNMB in placebo/control arms that was found. Bleeding risk is an important factor in deciding if anticoagulation should be extended and subsequently during follow-up to determine continued safety of extended anticoagulation. The aforementioned guidelines urge clinicians to annually re-evaluate the need for extended VTE treatment and suggest that elevation in bleeding risk or changes in patient preference may be reason to discontinue anticoagulation.

In this NMA, aspirin did not significantly decrease recurrent VTE risk compared to placebo. The two trials evaluating aspirin for extended VTE treatment presented conflicting evidence themselves.[14,15] WARFASA demonstrated a significant reduction in recurrent VTE when aspirin was used for a median of 23.9 months compared to placebo [hazard ratio (HR) 0.58 (0.36 to 0.98)] while the results of APSPIRE did not reach statistical significance for this outcome after a median of 37.2 months [HR 0.74 (0.52 to 1.05)]. Results of INSPIRE, an individual-patient-data meta-analysis of these two trials, demonstrated a statistically significant reduction in VTE recurrence with aspirin versus placebo [HR 0.68 (0.51 to 0.90)] over a median treatment period of 30.4 months.[20] Annual major bleeding rate was similar in the aspirin and placebo groups (0.5% vs. 0.4%, respectively). Findings from INSPIRE suggest that although less profound of an effect in reducing recurrent VTE compared to anticoagulants, aspirin remains an

option for further VTE protection in patients with unprovoked VTE after initial anticoagulant treatment.[20] Potential clinical scenarios include patients with bleeding risk that has increased to an unacceptable level or patients who may change their preference over time.

A prior NMA by Castellucci et. al.[21] concluded that extended VTE treatment with oral anticoagulants or antiplatelets reduced recurrent VTE risk compared to placebo or observation, although the reduction associated with aspirin did not reach statistical significance. Major bleeding was increased with either VKAs or dabigatran compared to placebo or observation. Our literature base differed from this prior NMA in several ways although this did not seem to translate into differences in overall conclusions with exception of dabigatran's impact on major bleeding, which was not significantly increased compared to placebo in our analysis. Castellucci et al. included trials that evaluated ximelagatran and low-intensity warfarin which we did not include in our network based on contemporary practice options. We also required trials to perform randomization after completion of the acute treatment phase in order to be included in our NMA and we allowed inclusion of idraparinux.

Our analysis is unique from the prior NMA in that individual components of composite outcomes were also evaluated separately, and we evaluated the more contemporary bleeding outcome CRNMB. These analyses add to the clinical utility of the results since patients and clinicians may place differing values on the individual components of the composite outcomes and now can appreciate the relative contribution of each individual outcome in the overall reduction in VTE risk or increase in composite bleeding risk. In addition, we have a novel network focusing on newer anticoagulants, albeit a post-hoc analysis, that supported the findings from the primary network.

The results of this NMA should be considered in the context of its limitations. We were limited in our ability to evaluate statistical heterogeneity due to the small number of trials within each pair-wise comparison, or lack of greater than one trial. Similarly, our evaluation of consistency is limited since there were few instances where both direct and indirect data were available for a given comparison. Both evaluation of heterogeneity and consistency are subject to type I and type II error, and given the small size of the network, type II error cannot be ruled out.[22] An additional limitation due to the size of the network both in terms of overall number of trials and number of trials within each direct pairwise comparison is the relative width of confidence intervals accompanying our results. We evaluated individual components of the primary outcomes although for some outcomes results were also hindered by the small number of trials and events per pairwise comparison contributing to the imprecision observed. Although our data supports extended anticoagulation at large, our analysis was not able to identify an optimal duration, since the trials used treatment periods ranging from 6 months to 4 years. Finally, to truly appreciate how differences in the baseline risk of VTE recurrence in the studied population impacts outcomes, an individual patient data meta-analysis would be ideal.

In summary, extended anticoagulation in VTE treatment is a reasonable strategy for long-term risk reduction of VTE recurrence. While most evaluated therapies were efficacious in reducing VTE recurrence relative to placebo, apixaban has an advantageous bleeding profile and may be preferentially selected for extended VTE treatment.

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Table 1. Baseline characteristics of included randomized controlled trials

Trial	Randomized intervention (n)	Duration of follow-up*	Males N (%)	Age y (SD)	Index event N (%)	Unprovoked Index Event N (%)	Prior VTE N (%)	TTR %
AMPLIFY-EXT N=2486	Apixaban 2.5mg BID X 12m (n=840)	12m	487 (58.0)	56.6 (15.3)	DVT: 544 (64.8) PE: 296 (35.2)	783 (93.2)	99 (11.8)	NA
	Apixaban 5mg BID X 12m (n=813)		469 (57.7)	56.4 (15.6)	DVT: 527 (64.8) PE: 286 (35.2)	737 (90.7)	118 (14.5)	
	Placebo X 12m (n=829)		468 (56.5)	57.1 (15.2)	DVT: 551 (66.5) PE: 278 (33.5)	755 (91.1)	99 (11.9)	
RESONATE N=1343	Dabigatran 150mg BID X 6m (n=681)	6m	381 (55.9)	56.1 (15.5)	DVT: 431 (63.3) PE: 183 (26.9) Both: 47 (6.9)	NR	2 (0.3)	NA
	Placebo X 6m (n=662)		364 (55.0)	55.5 (15.1)	DVT: 441 (66.6) PE: 178 (26.9) Both: 35 (5.3)		0 (0)	
REMEDY N=2856	Dabigatran 150mg BID X 6-36m (n=1430)	18m	871 (60.9)	55.4 (15.0)	DVT:938 (65.6) PE: 324 (22.7) Both: 167 (11.7)	NR	13 (0.9)	
	Warfarin daily X 6-36m (n=1426)		871 (61.1)	53.9 (15.3)	DVT: 922 (64.7) PE: 335 (23.5) Both: 168 (11.8)		13 (0.9)	TTR: 65.3 Above: 12.2 Below: 17.3
WARFASA N=403	Aspirin 100mg daily x 2y (n=205)	23.9m[&]	135 (65.8)	61.9 (15.3)	DVT: 122 (59.5) PE: 83 (40.5)	205 (100)	NR	NA
	Placebo x 2y (n=197)		122 (61.9)	62.1 (15.1)	DVT: 130 (65.9) PE: 67 (34.1)	197 (100)	NR	

Trial	Randomized intervention (n)	Duration of follow-up*	Males N (%)	Age y (SD)	Index event N (%)	Unprovoked Index Event N (%)	Prior VTE N (%)	TTR %
ASPIRE N=822	Aspirin 100mg daily X 2-4y (n=411)	37.2m[&]	226 (55.0)	55.0 (16.0)	DVT: 236 (57.0) PE: 112 (27.0) Both: 59 (14.0)	411 (100)	41 (5)[#]	NA
	Placebo X 2-4y (n=411)		221 (54.0)	54.0 (15.8)	DVT: 232 (56.0) PE: 119 (29.0) Both : 56 (14.0)	411 (100)		
EINSTEIN-EXT N=1197	Rivaroxaban 20mg daily X 6 or 12m (n=602)	6-12m	354 (58.8)	58.2 (15.6)	DVT: 386 (64.1) PE: 216 (35.9)	440 (73.1)	108 (17.9)	NA
	Placebo X 6 or 12m (n=594)		339 (57.1)	58.4 (16.0)	DVT: 356 (59.9) PE: 238 (40.1)	441 (74.2)	84 (14.1)	
AUREC-FVII N=34	VKA x 2y (n=17)	2y	5 (29)	53.0 (18.0)	DVT: 9 (53) PE +/- DVT: 8 (47)	17 (100)	0 (0)	NR
	No VKA X 2y (n=17)		6 (35)	54.0 (16.0)	DVT: 11 (65) PE +/- DVT: 6 (35)	17 (100)	0 (0)	
Vitovec, 2009 N=52	Warfarin X 6m (n=27)	6m	24 (46.2)[#]	58.0 (12.0)[#]	DVT: 27 (100)	27 (100)	0 (0)^	NR
	No warfarin (n=25)				DVT: 25 (100)	25 (100)	0 (0)^	
Van Gogh N=1217	Idraparinux 2.5mg SQ weekly X 6m (n=594)	6m	317 (53.4)	60.2 (15.2)	DVT: 332 (55.9) PE: 283 (47.6)	364 (61.3)	109 (18.4)	NA
	Placebo X 6m (n=621)		326 (52.5)	59.9 (15.4)	DVT: 337 (54.3) PE: 304 (49.0)	371 (59.7)	112 (18.0)	

Trial	Randomized intervention (n)	Duration of follow-up*	Males N (%)	Age y (SD)	Index event N (%)	Unprovoked Index Event N (%)	Prior VTE N (%)	TTR %
WODIT-DVT N=267	OAC X 9m (n=134)	9m	73 (54.5)	66.8 (6.7)	DVT: 134 (100)	134 (100)	0 (0)	TTR: 81 Above: NR Below: NR
	No OAC (n=133)		81 (61.2)	67.7 (7.3)	DVT: 133 (100)	133 (100)	0 (0)	
WODIT-PE N=326	VKA x 3 or 9m (n=165)	9m	65 (39.4)	62.9 (16.3)	PE: 72 (44.7) Both: 91 (55.2)	90 (55.9)	0 (0)	TTR: 83 Above: NR Below: NR
	No VKA (n=161)		67 (41.6)	61.0 (15.5)	PE: 74 (44.8) Both: 89 (55.3)	91 (56.5)	0 (0)	
Kearon, 1999 N=162	Warfarin X 24m (n=79)	10m[@]	54 (68)	59 (16)	DVT: 60 (76) PE: 19 (24)	79 (100)	5 (6)	TTR: 64 Above: 14 Below: 22
	No warfarin (n=83)		44 (53)	58 (16)	DVT: 61 (73) PE: 22 (27)	83 (100)	3 (4)	

* Reflects follow-up on treatment
[&] median
[@] mean
[#] Reflects total study population
[^] Prior DVT

Abbreviations: d=days; BID=twice a day; m=months; mg=milligrams; NR=not reported; OAC=oral anticoagulant; SD=standard deviation; TTR=time in therapeutic range; VKA=vitamin k antagonist; VTE=venous thromboembolism; w=weeks

Table 2. Network meta-analysis results of the effect of extended venous thromboembolism treatment referent to placebo

	DVT	PE	Non-fatal PE	Fatal PE	Mortality	Major bleeding	CRNMB
Apixaban 2.5mg	**0.11** (0.05 to 0.26)	NA	0.53 (0.12 to 1.25)	0.28 (0.06 to 1.35)	0.49 (0.20 to 1.21)	0.49 (0.09 to 2.65)	1.30 (0.72 to 2.33)
Apixaban 5mg	**0.15** (0.07 to 0.32)	NA	**0.27** (0.09 to 0.82)	0.44 (0.11 to 1.69)	**0.29** (0.10 to 0.87)	0.25 (0.03 to 2.28)	**1.82** (1.05 to 3.15)
Aspirin	0.77 (0.55 to 1.08)	0.77 (0.37 to 1.59)	0.65 (0.41 to 1.03)	0.98 (0.14 to 6.92)	0.95 (0.53 to 1.70)	1.28 (0.48 to 3.44)	1.70 (0.55 to 5.22)
Dabigatran	**0.08** (0.02 to 0.30)	NA	**0.15** (0.03 to 0.69)	0.35 (0.01 to 23.91)	0.26 (0.04 to 1.66)	2.48 (0.63 to 9.74)	NA
Idraparinux	0.29 (0.08 to 1.02)	**0.26** (0.07 to 0.92)	**0.10** (0.01 to 0.73)	2.10 (0.19 to 22.90)	2.34 (0.72 to 7.58)	**23.81** (1.42 to 400.35)	NA
Rivaroxaban	**0.16** (0.06 to 0.41)	NA	**0.15** (0.03 to 0.67)	0.99 (0.06 to 15.70)	0.49 (0.04 to 5.37)	8.85 (0.48 to 164.08)	**4.53** (2.03 to 10.11)
Vitamin K antagonists	**0.06** (0.01 to 0.25)	0.18 (0.02 to 1.43)	**0.09** (0.02 to 0.43)	0.35 (0.01 to 8.54)	0.30 (0.05 to 1.82)	**4.64** (1.31 to 16.41)	NA

Values represent relative risks and 95% confidence intervals. Statistically significant results are in bold.

Abbreviations: CRNMB=clinically relevant non-major bleeding; DVT=deep vein thrombosis; NA=not applicable; PE=pulmonary

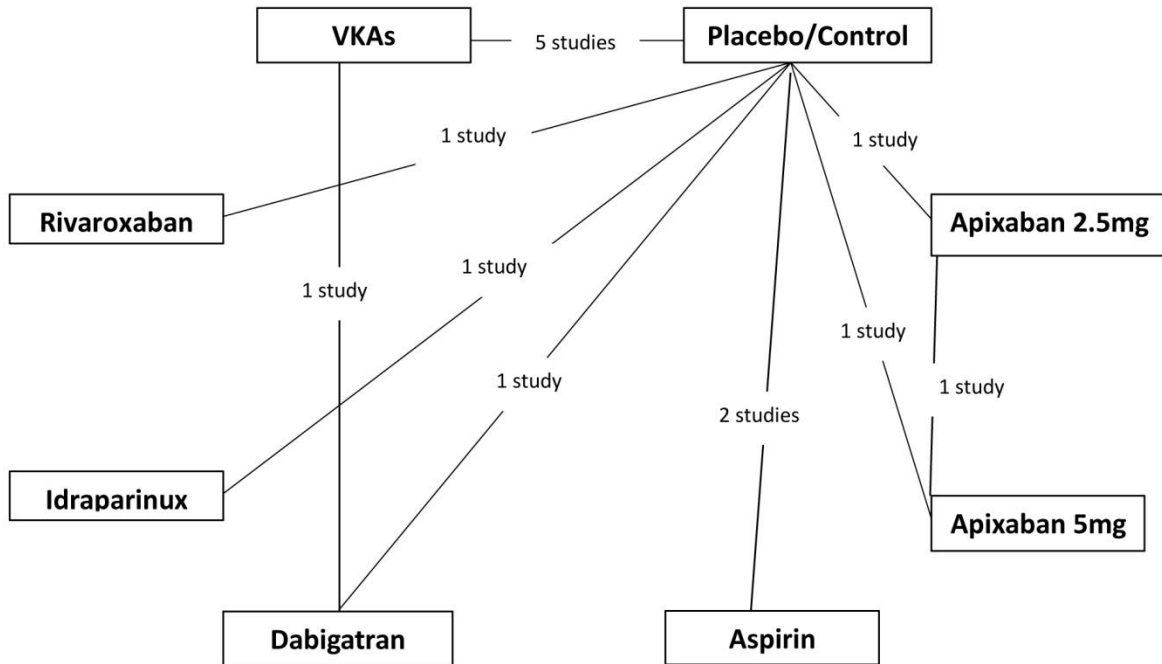embolism

Appendix A. Search strategy

1. venous thromboembolism.mp. or venous thromboembolism/

2. pulmonary embolism.mp. or pulmonary embolism/

3. deep vein thrombosis.mp. or venous thrombosis/

4. anticoagulants/ or (anticoagulant or warfarin or acenocoumarol or coumarins or aspirin or

   acetylsalicylic acid or acetyl salicylic acid or rivaroxaban or apixaban or dabigatran or

   edoxaban or vitamin K antagonists).mp.

5. 1 or 2 or 3

6. 4 and 5

7. limit 6 to humans

8. limit 7 to randomized controlled trial

Figure 1. Flow diagram of selected randomized controlled trials.
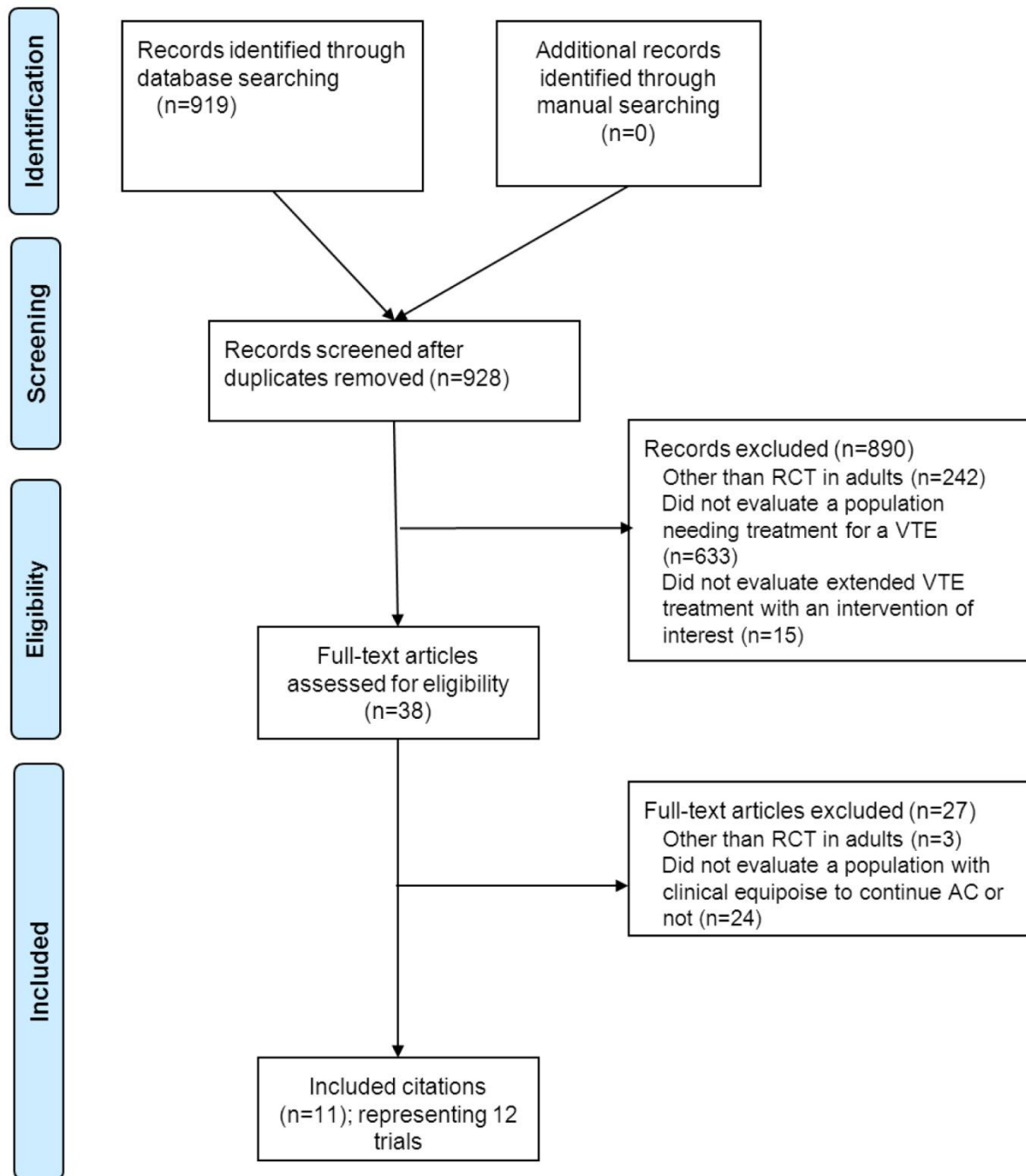
One published manuscript[13] reported two distinct randomized-controlled trials.

Figure 2. Network Diagram of Randomized Controlled Trials Evaluating Extended Venous Thromboembolism Treatment

Lines represent the presence of direct comparison trial(s).
Abbreviations: VKAs=vitamin K antagonists

Figure 3. Efficacy and Safety of Extended Treatment for Venous Thromboembolism

Apixaban 2.5mg	1.34 (0.82 to 2.18)	1.22 (0.49 to 3.04)	**2.39 (1.02 to 5.57)**	**2.56 (1.01 to 6.46)**	0.83 (0.48 to 1.43)	**4.18 (1.58 to 11.06)**	**4.35 (1.79 to 10.55)**
0.97 (0.38 to 2.48)	**Apixaban 5mg**	0.91 (0.37 to 2.25)	1.79 (0.77 to 4.12)	1.92 (0.77 to 4.78)	0.62 (0.36 to 1.05)	**3.13 (1.19 to 8.18)**	**3.25 (1.36 to 7.80)**
0.27 (0.10 to 0.71)	**0.28 (0.11 to 0.73)**	**Aspirin**	1.95 (0.74 to 5.18)	2.10 (0.74 to 5.95)	0.68 (0.33 to 1.41)	**3.42 (1.16 to 10.13)**	**3.56 (1.30 to 9.76)**
1.23 (0.35 to 4.31)	1.26 (0.36 to 4.44)	**4.54 (1.55 to 13.25)**	**Dabigatran**	1.07 (0.40 to 2.88)	**0.35 (0.18 to 0.66)**	1.75 (0.62 to 4.91)	**1.82 (1.41 to 2.35)**
0.70 (0.18 to 2.68)	0.72 (0.19 to 2.76)	2.58 (0.80 to 8.37)	0.57 (0.14 to 2.37)	**Idraparinux**	**0.32 (0.15 to 0.68)**	1.63 (0.55 to 4.88)	1.70 (0.61 to 4.71)
0.19 (0.08 to 0.43)	**0.20 (0.09 to 0.45)**	0.70 (0.43 to 1.16)	**0.16 (0.06 to 0.40)**	**0.27 (0.09 to 0.79)**	**Placebo**	**5.05 (2.26 to 11.29)**	**5.26 (2.62 to 10.54)**
1.01 (0.29 to 3.56)	1.04 (0.30 to 3.67)	**3.74 (1.28 to 10.97)**	0.82 (0.21 to 3.17)	1.45 (0.35 to 6.05)	**5.31 (2.05 to 13.79)**	**Rivaroxaban**	1.04 (0.36 to 3.01)
1.34 (0.40 to 4.49)	1.38 (0.41 to 4.63)	**4.95 (1.79 to 13.72)**	1.09 (0.51 to 2.31)	1.92 (0.48 to 7.67)	**7.03 (2.89 to 17.11)**	1.32 (0.36 to 4.88)	**VKA**

Results are the RR and 95% confidence interval of the column defining treatment in comparison to the row defining treatment. Results below the diagonal line of interventions reflect recurrent VTE risk whereas results above the diagonal line reflect risk of the composite bleeding outcome (major bleeding plus clinically relevant non-major bleeding). To obtain relative risks for comparisons in the opposite direction, take the reciprocal. Statistically significant results are in bold.

Abbreviations: CRNMB=clinically relevant non-major bleeding; VKA=vitamin K antagonist; VTE=venous thromboembolism

Figure 4. Post-hoc analysis of new oral anticoagulants only

Apixaban 2.5mg	1.34 (0.82 to 2.18)	**2.39 (1.02 to 5.57)**	0.83 (0.48 to 1.43)	**4.18 (1.58 to 11.06)**
0.97 (0.47 to 2.00)	**Apixaban 5mg**	1.79 (0.77 to 4.12)	0.62 (0.36 to 1.05)	**3.13 (1.19 to 8.18)**
2.41 (0.65 to 8.90)	2.48 (0.67 to 9.17)	**Dabigatran**	**0.35 (0.18 to 0.66)**	1.75 (0.62 to 4.91)
0.19 (0.11 to 0.34)	**0.20 (0.11 to 0.35)**	**0.08 (0.02 to 0.26)**	**Placebo**	**5.05 (2.26 to 11.29)**
1.01 (0.40 to 2.58)	1.04 (0.41 to 2.66)	0.42 (0.10 to 1.69)	**5.31 (2.52 to 11.19)**	**Rivaroxaban**

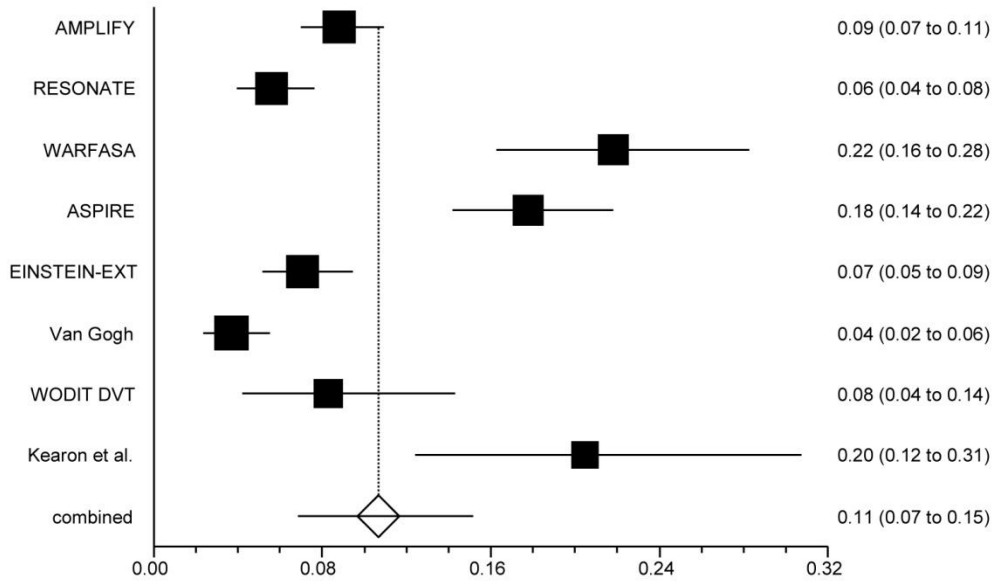Results are the RR and 95% confidence interval of the column defining treatment in comparison to the row defining treatment. Results below the diagonal line of interventions reflect recurrent VTE risk whereas results above the diagonal line reflect risk of the composite bleeding outcome (major bleeding plus clinically relevant non-major bleeding). To obtain relative risks for comparisons in the opposite direction, take the reciprocal. Statistically significant results are in bold.

Appendix Figure 1. Risk of bias assessment

	Random sequence generation	Allocation concealment	Blinding-participants and personnel	Blinding-outcome assessment	Incomplete outcome data	Selective outcome reporting
AMPLIFY	+	+	+	+	+	+
RESONATE	+	+	+	+	+	+
REMEDY	+	+	+	+	+	+
WARFASA	+	+	+	+	+	+
ASPIRE	+	+	+	+	+	+
EINSTEIN-EXT	+	+	+	+	+	+
AUREC-FVII	?	?	-	+	+	+
Vitovec, 2009	?	?	?	?	+	+
Van Gogh	+	+	+	?	+	+
WODIT-DVT	?	+	-	+	+	+
WODIT-PE	?	+	-	+	+	+
Kearon, 1999	+	+	+	?	+	+

The following symbols are used to denote low risk of bias (+), high risk of bias (-) and unclear risk of bias (?).

Appendix Figure 2. Proportion of patients with recurrent venous thromboembolism in placebo and untreated control arms of trials included in the base-case

AMPLIFY	0.09 (0.07 to 0.11)
RESONATE	0.06 (0.04 to 0.08)
WARFASA	0.22 (0.16 to 0.28)
ASPIRE	0.18 (0.14 to 0.22)
EINSTEIN-EXT	0.07 (0.05 to 0.09)
Van Gogh	0.04 (0.02 to 0.06)
WODIT DVT	0.08 (0.04 to 0.14)
Kearon et al.	0.20 (0.12 to 0.31)
combined	0.11 (0.07 to 0.15)

Proportion of patients experiencing the event during the trial follow-up period, with accompanying 95% confidence intervals.

Appendix Figure 3. Proportion of patients with major bleeding and clinically relevant non-major bleeding in placebo and untreated control arms of trials included in the base-case
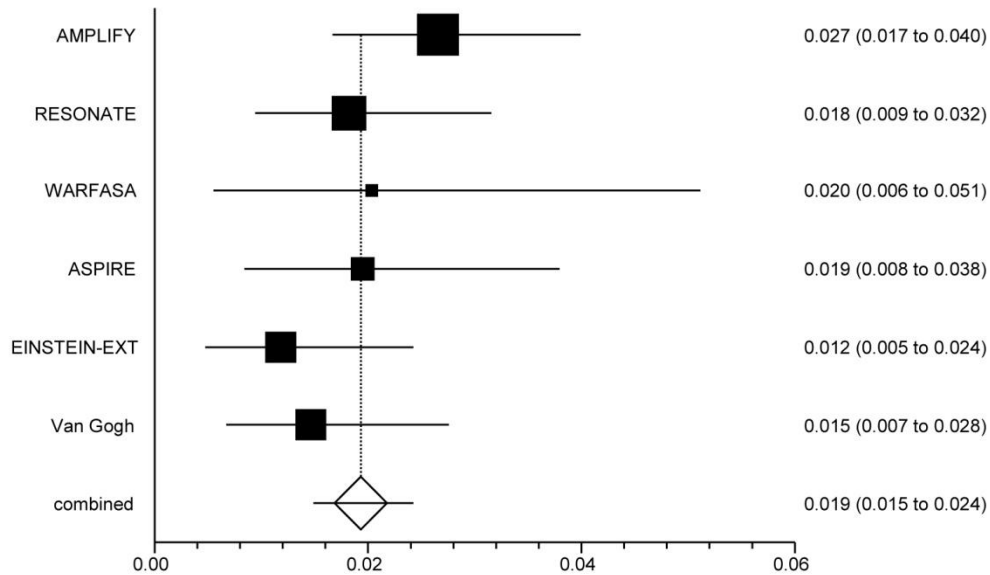
Proportion of patients experiencing the event during the trial follow-up period, with accompanying 95% confidence intervals.

Highlights

- We evaluated extended pharmacologic treatment of venous thromboembolism (VTE) through network meta-analysis.
- Extended treatment of VTE is a reasonable approach to provide continued protection from VTE recurrence.
- Bleeding risk is variable across therapeutic options.
- Apixaban, dabigatran, rivaroxaban, idraparinux and VKAs reduced VTE recurrence versus placebo.
- Apixaban appears to have a more favorable safety profile compared to other therapies.