Application to add Direct Oral Anticoagulants (DOAC) to WHO Model List of Essential Medicines

As a Medicine for Treatment of Non-Valvular Atrial Fibrillation and Treatment Venous Thromboembolism

Submitted by:

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Potential conflicts of interest

Dr. Neumann and Dr. Schünemann declare no conflict of interest

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General items

1. Summary statement of the proposal for inclusion, change or deletion.

This application proposes to add direct oral anticoagulants (DOACs, e.g. Dabigatran, Rivaroxaban, Apixaban and Edoxaban) to the complementary list of WHO Essential Medicine as treatment for:

1. Individuals with non-valvular atrial fibrillation who require anticoagulation
2. Individuals with venous thromboembolism.

Non-valvular atrial fibrillation and venous thromboembolism are major contributors to global disease burden. The use of anticoagulants is a very effective preventing strokes in individuals with non-valvular atrial fibrillation and recurrence of thrombosis in people with venous thromboembolism. For many years, the only anticoagulant available were vitamin K antagonists, which have a narrow therapeutic window and highly variable pharmacokinetics. Given these limitations, a large proportion of patients have poorly controlled anticoagulation with vitamin K antagonists, which is associated with an increased mortality and morbidity. In low and middle-income countries, the control of anticoagulation is even worse (compared to North America or Europe), and some patients who would benefit from anticoagulation do not receive it given their limited access to follow-up and monitoring.

The use of DOACs do not require dose monitoring, strict follow-up or changes to the diet or life-style. In individuals with atrial fibrillation, the use of DOACs instead of vitamin K antagonists probably reduce mortality, the risk of stroke and the risk of major bleeding. Whereas in individual with venous thromboembolism, DOACs are as effective as vitamin K antagonists, but with a lower risk of bleeding.

A number of economic evaluations show that the use of DOAC is cost effective compared to vitamin K antagonists, and in some settings, actually, may lead to a cost reduction.

DOAC are widely available, although in settings where there is no insurance or subsidization for medications, the current price of the drug is probably a barrier, which may lead to a scenario where affluent individuals are treated preferentially with DOACs and disadvantages population continue receiving vitamin K antagonists.
2. Relevant WHO technical department and focal point.

Pending

3. Name of organization(s) consulted and/or supporting the application.

Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada

WHO Collaborating Center for Evidence Informed Policy, McMaster University, Hamilton, Ontario, Canada

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

<table>
<thead>
<tr>
<th>International Nonproprietary Name (INN)</th>
<th>Anatomical Therapeutic Chemical (ATC) code</th>
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</thead>
<tbody>
<tr>
<td>Dabigatran etexilate</td>
<td>B01AE07</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>B01AF01</td>
</tr>
<tr>
<td>Apixaban</td>
<td>B01AF02</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>B01AF03</td>
</tr>
</tbody>
</table>
5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).

Dabigatran:
Manufacturer: Boehringer Ingelheim
Trade name: Pradaxa
Anticoagulation dose: 75 and 150 mg twice daily

Rivaroxaban:
Manufacturer: Bayer
Trade name: Xarelto
Anticoagulation dose: 15 mg twice daily and 20 mg once daily

Apixaban:
Manufacturer: Bristol-Myers Squibb
Trade name: Eliquis
Anticoagulation dose: 2.5 and 5 mg twice daily

Edoxaban:
Manufacturer: Daiichi Sankyo Company
Trade name: Savaysa and Lixiana
Anticoagulation dose: 30 and 60 mg once daily

There is no formulation for children or pregnant women.

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.
As individual medicines.
Treatment details, public health relevance and evidence appraisal and synthesis

7. Treatment details

Therapeutic dosage regimen for individual with non-valvular atrial fibrillation and venous thromboembolism (including special populations)

In general, in individuals with non-valvular atrial fibrillation at increased risk of stroke and in people with venous thromboembolism, the desirable effects of anticoagulation outweigh its potential risks (please see relevant recommendations and guidelines section)

Dabigatran:

*Non-valvular Atrial Fibrillation:*
- For patients with CrCl >30 mL/min: 150 mg orally, twice daily
- For patients with CrCl 15-30 mL/min: 75 mg orally, twice daily

*Venous Thromboembolism:*
- For patients with CrCl >30 mL/min: 150 mg orally, twice daily after 5-10 days of parenteral anticoagulation

Rivaroxaban:

*Non-valvular Atrial Fibrillation:*
- For patients with CrCl >50 mL/min: 20 mg orally, once daily
- For patients with CrCl 15-50 mL/min: 15 mg orally, once daily

*Venous Thromboembolism:*
- 15 mg orally twice daily for the first 21 days, then 20 mg orally once daily

Apixaban:

*Non-valvular Atrial Fibrillation:*
- The recommended dose is 5 mg orally twice daily
- In patients with at least 2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL, the recommended dose is 2.5 mg orally twice daily

*Venous Thromboembolism:*
- The recommended dose is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily

Edoxaban:

*Non-valvular Atrial Fibrillation:*
- For patients with CrCL >50 to ≤ 95 mL/min 60 mg once daily
For patients with CrCL 15 to 50 mL/min 30 mg once daily

**Venous Thromboembolism:**
For patients with CrCl >50 mL/min: 60 mg once daily
For patients with CrCl 15-50 mL/min, body weight less than or equal to 60 kg or who use P-gp inhibitors: 30 mg once daily

**Duration of treatment in individuals with non-valvular atrial fibrillation and venous thromboembolism**
As with the decision whether to initiate anticoagulation, the duration of treatment should be individualized to the specific clinical circumstances and patients’ values and preferences and it should be continuously reassessed. Anticoagulation may last a defined period of time (for example 3 to 6 months) or be an indefinite treatment (please see relevant recommendations and guidelines section)

**Relevant recommendations and guidelines**

We hand searched the websites of national guideline programs and relevant professional societies. We included in this report recommendations developed or updated on the last 4 years.

**Non-valvular Atrial Fibrillation**

**Summary:**
Recent guidelines recommend anticoagulation in individuals at increased risk of stroke. The population considered “at increased risk” is variable across guidelines, but prognostic score like CHADS and CHADS-VASc are commonly proposed to assess the individual risk. In older guidelines, DOACs are proposed as alternative to warfarin, while in more recent recommendations, DOACs are suggested as the preferred option.

1. **American Heart Association Guidelines (2014) (1):**
Anticoagulation is recommended in individuals at increased risk of stroke. Dabigatran, rivaroxaban and apixaban are proposed as alternative to VKA.

Relevant recommendations:

In patients with AF, antithrombotic therapy should be individualized based on shared decision making after discussion of the absolute and relative risks of stroke and bleeding and the patient’s values and preferences. (Level of Evidence: C)

For patients with nonvalvular AF with prior stroke, transient ischemic attack (TIA), or a CHA2DS2-VASc score of 2 or greater, oral anticoagulants are recommended. Options include warfarin (INR 2.0 to 3.0), dabigatran, rivaroxaban, or apixaban.
Anticoagulation is recommended in individuals at increased risk of stroke. Dabigatran, rivaroxaban and apixaban are preferred over VKA.

Relevant recommendations:
If the patient has stable CAD/vascular disease and is aged ≥ 65 years or the CHADS2 score ≥ 1, we recommend OAC therapy alone (Strong Recommendation, High-Quality Evidence).

When OAC is indicated, a DOAC is recommended in preference to a VKA for non-valvular AF

Anticoagulation is recommended in individuals at increased risk of stroke. Dabigatran, rivaroxaban and apixaban are proposed as alternative to VKA.

Relevant recommendations:
Anticoagulation may be with apixaban, dabigatran etexilate, rivaroxaban or a vitamin K antagonist.

Consider anticoagulation for men with a CHA2DS2-VASc score of 1. Take the bleeding risk into account (conditional recommendation)

Offer anticoagulation to people with a CHA2DS2-VASc score of 2 or above, taking bleeding risk into account (strong recommendation)

Discuss the options for anticoagulation with the person and base the choice on their clinical features and preferences.

Anticoagulation is recommended in individuals at increased risk of stroke. Dabigatran, rivaroxaban and apixaban are preferred over VKA.

Relevant recommendations:
Oral anticoagulation therapy to prevent stroke and systemic embolism should be considered in patients with N-VAF whose CHA2DS2-VASc score is 1 (strong recommendation, moderate certainty evidence)
Oral anticoagulation therapy to prevent stroke and systemic embolism is recommended in patients with non-valvular AF (N-VAF) whose CHA2DS2-VASc score is 2 or more, unless there are contraindications to anticoagulation (strong recommendation, high certainty evidence).

When oral anticoagulation is initiated in a patient with N-VAF, a non-vitamin K oral anticoagulant (NOAC)—apixaban, dabigatran or rivaroxaban—is recommended in preference to warfarin (strong recommendation, moderate certainty evidence).

**Venous thromboembolism**

**Summary:**
Recent guidelines suggest short term anticoagulation in individual at low risk of recurrence and indefinite anticoagulation in people at high risk (e.g. unprovoked events). DOACs are suggested over VKA as the preferred alternative.

In individuals at low risk of recurrence, short term anticoagulation is recommended. Whereas in individuals at high risk of recurrence, the panel suggested indefinite anticoagulation. On both cases, DOAC are suggested as the preferred alternative.

Relevant recommendations:
In patients with deep venous thrombosis or pulmonary embolism, the ASH guideline panel suggests using Direct Oral Anticoagulants (DOAC) over Vitamin K Antagonists (VKA) (conditional recommendation based on moderate certainty in the evidence about effects).

In patients who develop a deep venous thrombosis or pulmonary embolism in relation with a transient risk factor and have history of a previous thrombotic event with a relative high risk of recurrence (unprovoked or provoked by a chronic risk factor), the ASH guideline panel suggests continuing anticoagulation over stopping anticoagulation after completion of an initial course of therapy (conditional recommendation based on moderate certainty in the evidence about effects).

In patients who develop a deep venous thrombosis or pulmonary embolism in relation with a transient risk factor and have history of a previous thrombotic event also related with a transient risk factor, the ASH guideline panel suggests stopping anticoagulation after completion of an initial course of therapy over continuing it indefinitely (conditional recommendation based on moderate certainty in the evidence about effects).
In patients with deep venous thrombosis or pulmonary embolism provoked by a chronic risk factor, the ASH guideline panel suggests continuing indefinite anticoagulation over stopping anticoagulation after completion of an initial course of therapy (conditional recommendation based on moderate certainty in the evidence about effects).

In patients with unprovoked deep venous thrombosis or pulmonary embolism, the ASH guideline panel suggests continuing indefinite anticoagulation over stopping anticoagulation after completion of an initial course of therapy (conditional recommendation based on moderate certainty in the evidence about effects).

In patients with a recurrent unprovoked deep venous thrombosis or pulmonary embolism, the ASH guideline panel recommends continuing indefinite anticoagulation over stopping anticoagulation after completion of an initial course of therapy (strong recommendation based on moderate certainty in the evidence about effects).

This guideline focused on individuals at high risk of recurrence. In this population, indefinite anticoagulation was suggested and DOAC was preferred over VKA.

Relevant recommendations:
In patients with deep venous thrombosis or pulmonary embolism, the ASH Latin American Guideline Panel suggests using Direct Oral Anticoagulants (DOAC) over Vitamin K Antagonist (VKA) (conditional recommendation based on moderate certainty in the evidence about effects).

In patients who develop a deep venous thrombosis or pulmonary embolism in relation with a transient risk factor and have history of a previous thrombotic event with a relative high risk of recurrence (unprovoked or provoked by a chronic risk factor), the ASH Latin American Guideline Panel suggests continuing anticoagulation over stopping anticoagulation after completion of an initial course of therapy (conditional recommendation based on moderate certainty in the evidence about effects).

In patients with unprovoked deep venous thrombosis or pulmonary embolism, the ASH Latin American Guideline Panel suggests continuing indefinite anticoagulation over stopping anticoagulation after completion of an initial course of therapy (conditional recommendation based on moderate certainty in the evidence about effects).

In patients with a recurrent unprovoked deep venous thrombosis or pulmonary embolism, the ASH Latin American Guideline Panel recommends continuing indefinite anticoagulation over stopping anticoagulation after completion of an initial course of therapy (conditional recommendation based on moderate certainty in the evidence about effects).
anticoagulation after completion of an initial course of therapy (strong recommendation based on moderate certainty in the evidence about effects)

8. Information supporting the public health relevance.

Global burden of Non-valvular Atrial Fibrillation
Non-valvular atrial fibrillation is the most common cardiac arrhythmia. The number of individuals with atrial fibrillation has been estimated in 33.5 million worldwide (7). Without antithrombotic treatment, the risk of stroke in patients with atrial fibrillation is around 5% per year, but it can be as high as 10% per year if other risk factors are present (8). In a cohort of 15,400 individuals with atrial fibrillation in 47 countries, the highest number of strokes occurred in patients in Africa (incidence 89/1137 [8%] per year), China (incidence 143/2023 [7%] per year), and Southeast Asia (incidence 88/1331 [7%] per year) (9).
In low and middle-income countries, stroke is associated with an increased mortality and significant disability, specially, in disadvantaged populations (10-12). Additionally, according to a recent WHO survey of 177 countries, provisions for the treatment and rehabilitation of patients with stroke are available in less than a quarter of public healthcare facilities in low and middle-income countries (13).

Global burden of Venous thromboembolism
Deep Venous Thrombosis and Pulmonary Embolism are major contributors to global disease burden. Their estimate incidence ranges from 0.7 to 2.7 per 1000 patients-year in Western Europe, 1.1 to 2.4 per 1000 patients-year in North America and 0.2 to 1.6 patients-year in Latin America and Asia (14). Additionally, venous thromboembolism markedly increases with age, with incidences as high as 4.29 to 5.64 per 1000 patients-year in individuals older than 70 years (15, 16). Thus, venous thromboembolism is likely to become an even more prominent problem with aging populations.

Current difficulties and inequities with the use of vitamin K antagonists
Anticoagulation, is a very effective treatment to prevent strokes in individuals with non-valvular atrial fibrillation and recurrence of thrombosis in people with venous thromboembolism. The relative risk reduction achieved with anticoagulation is 64% in atrial fibrillation (95% CI from 49% to 74%)(17) and 80% in venous thromboembolism (95% CI from 62% to 89%)(18).
For many years, the only anticoagulant available were vitamin K antagonists (e.g. warfarin), which have a narrow therapeutic window (i.e. a narrow range of blood concentration within is safe and effective) and a highly variable pharmacokinetics. Given these features, the use of vitamin K antagonists always require a strict follow-up and dose monitoring, as well many life-style and dietary changes.
In practice, a large proportion of community care patients have poorly controlled anticoagulation with vitamin K antagonists. In one study in Europe, the proportion of patients with poorly controlled treatment varied from 34.6% in the United Kingdom to 55.8% in Germany (19). The situation in low and middle income-countries is probably worst, as showed by a prospective cohort of patients with newly diagnosed atrial fibrillation, in whom the proportion of individuals with poor control reached 78% and 83% in Latin America and Asia compared with approximately 50% in North America and Europe (20).

As can be expected, poor anticoagulation is associated with worst outcomes. In the study by Hass et al, poor anticoagulation control was associated with an increased risk of stroke (HR 2.55, 95% CI 1.61 to 4.03), an increased risk of bleeding (HR 1.54, 95% CI 1.04 to 2.26) and a higher mortality (HR 2.39, 95% CI 1.87 to 3.06) (20).

Additionally, as suggested by a systematic review of strategies to improve stroke care, in low and middle-income countries an important proportion of patients not have access to regular follow-up and monitoring of the dose of vitamin K antagonists, which make physicians reluctant to start anticoagulation in patients who would benefit otherwise (21).

Finally, a recent observational study evaluating prescription patterns in individual with atrial fibrillation in the US suggested that the probability of receiving DOAC instead of vitamin K antagonists is higher in educated individuals (OR 1.43, 95% CI 1.31–1.56) and with high income (OR 1.36, 95% CI 1.27–1.45) (22). This pattern is probably even more accentuated in low and middle-income countries, although only anecdotal evidence was identified.


Non-valvular Atrial Fibrillation

Methods

We updated a systematic search from a previous application to the EML. We searched for systematic reviews from January 2016 to December 2018 on the following databases: MEDLINE, EMBASE, the Cochrane Library and Epistemonikos (detailed search strategy described on appendix). We used existing systematic review as a way to identify relevant trials, but we conducted our own meta-analyses

We used the following inclusion criteria:
1. Study design: randomized clinical trials
2. Population: Individuals with non-valvular atrial fibrillation
3. Intervention: Dabigatran, Rivaroxaban, Apixaban or Edoxaban
4. Comparison: Vitamin K Antagonists

We assessed the risk of bias using the Cochrane Collaboration Risk of Bias Tool (23). We also made judgments about precision, consistency, directness, and likelihood of publication bias following the GRADE approach (24).
We meta-analyzed the data using the Mantel–Haenszel method, random effect model. We assessed heterogeneity with the Chi-square test and with the I2 statistic. All the meta-analyses were conducted using RevMan (Version 5.3 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). We summarized the results on Summary of Findings (25) and Evidence to Decision Tables (26) using the software GRADEpro GDT (GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 developed by Evidence Prime, Inc.)

Results
We identified 8 systematic reviews (27-34) and 13 randomized trials (n=75,543) (35-47). Trials included individuals with atrial fibrillation and one or two additional risk factors for stroke (i.e. age ≥ 75 years; previous stroke, transient ischemic attack, or systemic embolism; symptomatic heart failure; diabetes mellitus; or hypertension requiring pharmacologic treatment). Participants were randomized to DOAC (doses as described above) or warfarin (target international normalized ratio 2.0 to 3.0) and were followed for 2 to 3 years. Individuals with estimated creatinine clearance of less than 30 ml per minute or a high risk of bleeding were excluded.

We found that the use of DOACs instead of VKA in individuals with non-valvular atrial fibrillation decreases mortality (RR 0.90, 95%CI 0.85-0.94, high certainty evidence) and the risk of stroke (RR 0.83, 95% CI 0.72-0.96, high certainty evidence). Also, probably decreases the risk of systemic embolism (RR 0.74, 95%CI 0.48-1.13, moderate certainty evidence) and major bleeding (RR 0.81, 95% CI 0.66-0.98, moderate certainty evidence). The results are summarized on table 1. In the appendix, we included the full GRADE evidence to decision framework and the forests plots of our meta-analyses.

Venous thromboembolism

Methods
In the context of the development of a clinical guideline regarding the management of venous thromboembolism for the American Society of Hematology, we conducted a search for systematic reviews on MEDLINE, EMBASE, the Cochrane Library and Epistemonikos from their respective date of inception to December 2018. Also, we conducted a search of potentially missed trials in MEDLINE and EMBASE from January 2015 to December 2018 (detailed search strategies described on appendix).

We used the following inclusion criteria:
1. Study design: randomized clinical trials
2. Population: Individuals with deep venous thrombosis or pulmonary embolism
3. Intervention: Dabigatran, Rivaroxaban, Apixaban or Edoxaban
4. Comparison: Vitamin K Antagonists
We excluded trials evaluating the effects of the direct thrombin inhibitor ximelagatran, given this drug was withdrawal from market due to safety concerns.

As before, we used existing systematic review as a way to identify relevant trials, but we conducted our own meta-analyses using the same methods described on the atrial fibrillation section.

**Results**

We identified 24 systematic reviews (48-71) and 12 randomized trials (n=28,876) (72-83). Trials included individuals with an objectively confirmed symptomatic proximal deep venous thrombosis or pulmonary embolism. Participants were randomized to DOAC (doses as described above) or to an initial treatment with low molecular weight heparin (5 to 10 days) followed by dose-adjusted warfarin (target international normalized ratio 2.0 to 3.0). Dabigatran was also administered after an initial treatment of 5 to 10 days with low molecular weight heparin, while rivaroxaban, apixaban and edoxaban were administered without initial parenteral anticoagulants. The length of the anticoagulation varied across trials from 3 to 12 months. Individuals with estimated creatinine clearance of less than 30 ml per minute or a high risk of bleeding were excluded.

Our analysis showed that the use of DOACs instead of VKA in individuals with deep venous thrombosis or pulmonary embolism likely has a small effect on mortality (RR 0.99, 95%CI 0.85-1.15, moderate certainty evidence) and the risk subsequent pulmonary embolism (RR 0.97, 95%CI 0.77-1.23, moderate certainty evidence). However, probably decreases the risk of a recurrent deep venous thrombosis (RR 0.80, 95%CI 0.59-1.09, moderate certainty evidence) and major bleeding (RR 0.63, 95%CI 0.47-0.84, high certainty evidence). Table 2 summarized the findings. In the appendix, we included the full evidence to decision framework and the forests plots of our meta-analyses.
Table 1 - DOAC compared to VKA for Non-valvular Atrial Fibrillation

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>№ of participants (studies) Follow-up</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects</th>
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<td></td>
<td>Risk with VKA</td>
</tr>
<tr>
<td>Death</td>
<td>73641 (13 RCTs)</td>
<td>⬤⬤⬤⬤ HIGH</td>
<td>RR 0.90 (0.85 to 0.94)</td>
<td>75 per 1,000</td>
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<tr>
<td>Stroke</td>
<td>75543 (13 RCTs)</td>
<td>⬤⬤⬤⬤ HIGH a</td>
<td>RR 0.83 (0.72 to 0.96)</td>
<td>33 per 1,000</td>
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<tr>
<td>Systemic Embolism</td>
<td>75018 (13 RCTs)</td>
<td>⬤⬤⬤◯ MODERATE b,c</td>
<td>RR 0.74 (0.48 to 1.13)</td>
<td>3 per 1,000</td>
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<tr>
<td>Major Bleeding</td>
<td>75490 (13 RCTs)</td>
<td>⬤⬤⬤◯ MODERATE d</td>
<td>RR 0.81 (0.66 to 0.98)</td>
<td>59 per 1,000</td>
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Explanations
a. Some heterogeneity was detected (I²=47%). We did not downgrade by inconsistency
b. Some heterogeneity was detected (I²=31%). We did not downgrade by inconsistency
c. The confidence interval probably crosses decision thresholds, therefore do not exclude potential benefit or harm relevant for patients
d. Significant heterogeneity was detected (I²=77%).

Table 2 - DOAC compared to VKA for Patients with DVT or PE

<table>
<thead>
<tr>
<th>+Outcomes</th>
<th>№ of participants (studies) Follow-up</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects</th>
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<td>Risk with VKA</td>
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<tr>
<td>Mortality</td>
<td>28778 (12 RCTs)</td>
<td>⬤⬤◯ MODERATE a</td>
<td>RR 0.99 (0.85 to 1.15)</td>
<td>Study Population - 1 year</td>
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<td>39 per 1,000</td>
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<tr>
<td>Pulmonary Embolism</td>
<td>28571 (12 RCTs)</td>
<td>⬤⬤◯ MODERATE a</td>
<td>RR 0.97 (0.77 to 1.23)</td>
<td>Study Population - 1 year</td>
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<td>20 per 1,000</td>
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<tr>
<td>Proximal Deep Venous Thrombosis</td>
<td>28668 (12 RCTs)</td>
<td>⬤⬤◯ MODERATE a</td>
<td>RR 0.80 (0.59 to 1.09)</td>
<td>Study Population - 1 year</td>
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<td>26 per 1,000</td>
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<tr>
<td>Major Bleeding</td>
<td>28876 (12 RCTs)</td>
<td>⬤⬤⬤ HIGH b</td>
<td>RR 0.63 (0.47 to 0.84)</td>
<td>Study population</td>
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<td>17 per 1,000</td>
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Explanations
a. Confidence interval around absolute estimates are wide and do not rule out potential benefit or harm important to patients
b. Some heterogeneity was observed (I²=31%), however we did not rate down for inconsistency
Bleeding risk

The main concern with the use of anticoagulants is the risk of bleeding. However, as described in the previous sections and tables 1 and 2, randomized trials suggest that the use of DOACs probably results in a lower risk of bleeding than with VKA (please see table 1 and 2).

Some recent large observational studies on “real world” populations suggest that the risk of bleeding with DOAC may be equivalent to the risk with VKA, while others studies suggest that, actually, it may be lower:

- A large cohort of 156,005 adults with atrial fibrillation and venous thromboembolism in the United Kingdom suggested a lower risk of bleeding with apixaban in comparison with warfarin (HR 0.69, 95% CI 0.54-0.79 in individuals with atrial fibrillation; HR 0.60, 95% CI 0.46 to 0.79 in individuals without atrial fibrillation). Also, investigators observed no significant differences on the risk of bleeding on the comparisons rivaroxaban versus warfarin (HR 1.12, 95% CI 0.99 to 1.26 in individuals with atrial fibrillation; HR 0.95, 95% CI 0.82 to 1.10 in individuals without atrial fibrillation) and dabigatran versus warfarin (HR 0.87, 95% CI 0.72 to 1.04 in individuals with atrial fibrillation; HR 0.98, 95% CI 0.71 to 1.35 in individuals without atrial fibrillation) (84).

- A propensity-matched analysis of 76,940 individuals with non-valvular atrial fibrillation of an administrative database from the United States suggested a lower risk of bleeding with apixaban in comparison to warfarin (HR: 0.60, 95% CI: 0.54-0.65) (85).

- A community-based population study of 59,525 adults with venous thromboembolism in Canada and the United States showed a similar risk of bleeding with DOAC and VKA (HR 0.99, 95% CI 0.84 to 1.16) (86).

- A propensity score matched analysis of 45,361 patients with non-valvular atrial fibrillation of an administrative database from the United States, showed a lower risk of bleeding with dabigatran (HR 0.69m 95% CI 0.50-0.96) and apixaban (HR 0.53, 95% CI 0.39-0.71) in comparison to warfarin. On patients using rivaroxaban, investigators observed a similar risk of bleeding in comparison to warfarin (HR 0.98, 95% CI: 0.83-1.17) (87).

- A propensity-matched cohort of 29,963 adults with venous thromboembolism in Denmark, also suggested a similar risk of bleeding with DOAC and VKA (HR 1.19, 95% CI 0.66 to 2.13)(88).

Emergency reversal of anticoagulation
The effects of VKA can be reversed with the administration of Four-Factor Prothrombin Complex Concentrate (or Fresh Frozen Plasma if is the latter is not available) plus the administration of intravenous Vitamin K.

On the other hand, DOAC require specific antidotes:

**Idarucizumab:**

It is a monoclonal antibody fragment that binds specifically to dabigatran. The clinical effectiveness of idarucizumab was assessed by the RE-VERSE AD trial. This study was an open label non-randomized trial of dabigatran users with a life-threatening bleeding (group A) or about to undergo an urgent procedure (group B). All participants received 5 g of intravenous idarucizumab. The results showed that anticoagulation was completely reverted in 98% of the patients within 4 hours (measured as normalization of diluted thrombin time or ecarin clotting time). In group A, bleeding cessation was observed in 134 of 203 patients. Of the remaining 69 patients on group A, in 2 bleeding stopped before receiving idarucizumab and in 67 it was not possible to assess the bleeding status. Of the 197 patients in group B, periprocedural haemostasis was judged as normal by clinicians in 184 patients, mildly abnormal in 10, and moderately abnormal in the remaining 3 (89).

**Andexanet Alfa:**

It is an inactive variant of factor Xa that binds to rivaroxaban, apixaban and edoxaban with high affinity. It was recently approved as antidote for rivaroxaban and apixaban based on the results of two open label randomized trials in healthy volunteers and the preliminary results of a non-randomized trial in factor Xa inhibitors users with acute major bleeding. At the date of elaboration of this report, andexanet alfa has not been licenced as antidote for edoxaban.

The ANNEXA-R and ANNEXA-A trials randomized healthy volunteers to rivaroxaban (ANNEXA-R, n=53) or placebo and to apixaban or placebo (ANNEXA-A, n=48). Participants received rivaroxaban or apixaban for 4 days and after the last dose on day fourth received andexanet (to revert rivaroxaban: 800-mg intravenous bolus followed by a continuous infusion of 8 mg per minute for 120 minutes; to revert apixaban: 400-mg intravenous bolus followed by a continuous infusion of 4 mg per minute for 120 minutes). The primary outcome of both trials was anti–factor Xa activity measured with a chromogenic assay. The results showed a reduction of anti–factor Xa activity of 92±11% with andexanet vs. 18±15% with placebo in the rivaroxaban study and a reduction of 94±2% with andexanet vs. 21±9% with placebo in the apixaban study (90).

There is an ongoing open-label, non-randomized trial (ANNEXA-4) evaluating the effects of andexanet on clinical endpoints in patients with acute bleeding under treatment with rivaroxaban or apixaban. In an interim report of this study, of the 47 patients available for analysis, 37 were judged as having good hemostasis by an independent adjudication committee (91).
Patients with atrial fibrillation and prosthetic heart valves

According to the data available to date, the use of DOAC is contraindicated in patients with mechanical prosthetic valves. This is based on the results of the RE-ALIGN trial, in which patients with atrial fibrillation and prosthetic heart valves were randomized to dabigatran (150, 220, or 300 mg twice daily) or warfarin. The trial was terminated prematurely after the enrolment of 252 patients given a higher incidence of stroke and major bleeding on the patients randomized to dabigatran (92).

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.

Price of DOACs

In the context of the development of the American Society of Hematology Guidelines and the Latin American version of the same guidelines, we hand-searched the references of economic evaluations and relevant websites to determine the price of DOACs in North America and Latin-America. For this report, we also hand-searched the references of the identified economic evaluations and relevant websites to add the price of DOACs in other territories when possible. We only included reliable sources, such as prices described on the literature and the prices published on official websites.

North America:

US and Canada: (5)
Dabigatran: $300.44–600.88 USD per month
Rivaroxaban: $300.42–600.84 USD per month
Apixaban: $300.44–600.88 USD per month

Latin America:

Argentina: (6)
Dabigatran: $1,602 Argentine Pesos per month (approximately 50 USD per month)
Rivaroxaban: $5,382 Argentine Pesos per month (approximately 150 USD per month)

Brazil: (6)
Dabigatran: $68.1 Reales per month (approximately 20 USD per month)
Rivaroxaban: $68.1 Reales per month (approximately 20 USD per month)

Chile: (6)
Dabigatran: $19,500 Chilean Pesos per month (approximately 30 USD per month)
Rivaroxaban: $44,040 Chilean Pesos per month (approximately 65 USD per month)

Colombia: (6)
Dabigatran: $ 95,520 Colombian Pesos per month (approximately 30 USD per month)
Rivaroxaban: $ 208,500 Colombian Pesos per month (approximately 65 USD per month)

Europe:

UK: (93)
Dabigatran: $ £68.8 per month (approximately 90 USD per month)
Rivaroxaban: $ £68.8 per month (approximately 90 USD per month)
Apixaban: $ £68.8 per month (approximately 90 USD per month)
Edoxaban: $ £68.8 per month (approximately 90 USD per month)

Oceania:

Australia: (94)
Dabigatran: $ 88.62 Australian Dollars per month (approximately 65 USD per month)
Rivaroxaban: $ 87.41 Australian Dollars per month (approximately 60 USD per month)
Apixaban: $ 93.16 Australian Dollars per month (approximately 68 USD per month)

Economic evaluations

Non-valvular Atrial Fibrillation
We conducted an electronic search in MEDLINE for systematic reviews of economic evaluations of any DOAC versus VKA in individuals with atrial fibrillation. We identified 2 systematic reviews. The first article identified was a systematic review of cost-utility analyses of dabigatran, rivaroxaban or apixaban versus warfarin. This review included 18 primary studies conducted in North America and Europe. All but one used a Markov model to extrapolate long-term data basing the calculation on the effectiveness and safety results from landmark trials. The majority of the models used the perspective of the payer. Thirteen models compared dabigatran versus warfarin, four rivaroxaban versus warfarin and four apixaban versus warfarin. Although there was some inconsistency among the conclusions of the individual models, the large majority showed that DOACs were cost-effective with ICERs below the willingness to pay thresholds and sometimes dominant over warfarin (95).

The second article identified was a systematic review of cost-utility analyses of apixaban versus warfarin. This review identified 26 primary studies conducted in North America, Latin America and Europe. All the studies except of one used a Markov model to extrapolate long-term data with the effectiveness and safety results from landmark trials. The majority of the models used the perspective of the payer with a lifetime horizon. The results showed that apixaban was cost-effective with ICERs below the willingness to pay thresholds (96).
Venous thromboembolism

In the context of the development of the American Society of Hematology Guidelines we conducted a systematic review of economic evaluations addressing the comparison DOACs vs VKA. We identified 5 cost comparisons between DOACs and VKA for patients with venous thromboembolism. Four reports suggested that DOAC is cost-saving compared with warfarin (97-100) and one study found an equivalent cost between DOAC and VKA. (101)
Also, we identified 14 economic evaluations comparing the cost and effectiveness of DOACs versus VKA. All of them suggested that DOACs is cost-effective compared to VKA. (98, 102-114)

Details of the Studies identified:
Cost comparisons:
Amin et al. 2014 (98)
An analysis in a hypothetical health plan population of 1 million members. Costs were reduced when DOACs are used instead of warfarin for the treatment of VTE, with apixaban being associated with the greatest reduction in medical costs.

Amin et al. 2016 (97)
A cost analysis based on real-world data. The study suggested that if DOACs were used instead of warfarin for acute VTE treatment, annual medical costs would be reduced. The greatest reduction would be for apixaban, followed by rivaroxaban, edoxaban, and dabigatran.

Courtney et al. 2016 (101)
A cohort based economic evaluation that compared 24 patients treated with rivaroxaban versus 24 matched patients treated with warfarin for provoked DVT. The cost per person on rivaroxaban was €273.30 versus €260.68 with warfarin. This analysis was done from the perspective of the Irish Healthcare system.

Margolis et al. 2016 (99)
A cost comparison based on matched cohorts of 751 patients with pulmonary embolism treated with rivaroxaban versus 751 patients treated with warfarin. This analysis suggested that rivaroxaban is cost-saving compared with warfarin.

Weeda et al. 2016 (100)
A cost comparison based on retrospective review of electronic health records and hospital billings. This analysis also suggested that rivaroxaban was associated with lower hospital treatment costs versus warfarin for patients with pulmonary embolism.
**Cost effectiveness analyses:**

Amin et al. 2014 (98)

A decision analytic model from US payer’s perspective in which DOACs was associated with less cost and lower risk of major bleedings and recurrent VTE compared with VKA. Apixaban was associated with the greater reduction in medical costs.

Bamber et al. 2015 (102)

A Markov model from the UK National Health Service perspective comparing rivaroxaban and VKA for the treatment of VTE. The analysis suggested that rivaroxaban was cost-effective. This result was robust across most of the assumptions.

Jimenez et al. 2015 (103)

A Markov model from the UK National Health Service perspective assessing the cost-effectiveness of rivaroxaban versus warfarin for the treatment of VTE. The analysis suggested that treatment with rivaroxaban costs less and was associated with more QALYs.

Jugrin et al. 2015 (104)

A decision analytic model conducted from UK National Health Service perspective. The results suggested that dabigatran was a cost-effective alternative to VKA in the acute treatment of VTE and in the extended anticoagulation.

Lanitis et al. 2016 (105)

A Markov model evaluating the cost-effectiveness of 6 months of treatment with apixaban versus other anticoagulants over a lifetime horizon from the perspective of the UK National Health Service. The results suggested that apixaban was cost-effective compared to warfarin.

Law et al. 2016 (106)

A chart review of VTE cases at two hospitals from the perspective of payers and patients. The analysis suggested that the use of DOAC was a cost-effective strategy in comparison to warfarin.

Lefebvre et al. 2014 (107)

A Markov model from a US payer perspective. In the base case analysis, rivaroxaban cost $2,448 less per patient and was associated with 0.0058 more QALYs compared with VKA.

Maervoet et al. 2015 (108)

A Markov model comparing rivaroxaban versus VKA for the treatment of DVT in Belgium. The analysis suggested that rivaroxaban was the dominant option for patients with DVT requiring three to six months of treatment and it was cost-effective for patients requiring twelve months of therapy.
Preblick et al. 2015 (109)
A cost-effectiveness model from a US health-care delivery system perspective using patient-level data from the Hoskusai-VTE trial. The analysis suggested that edoxaban was a cost-effective alternative to warfarin for the treatment of VTE.

Quon et al. 2016 (110)
A Markov model from the Ministry of Health Perspective in the Canadian setting. The analysis suggested that extended treatment with apixaban compared to warfarin resulted in fewer recurrent VTEs, VTE related deaths, and bleeding events, but with slightly increased cost. However, extended treatment with apixaban was cost-effective compared to warfarin.

Rudakova et al. 2015 (111)
A Markov model on Russian setting. According to this study, apixaban was a cost-effective alternative to warfarin for VTE treatment.

Santos et al. 2014 (112)
A Markov model conducted from the Portuguese societal perspective. The analysis suggested that, in patients with VTE, rivaroxaban cost less and resulted in more QALYs in comparison with warfarin.

Seaman et al. 2013 (113)
A Markov model from a societal perspective in the US setting. The results suggested that rivaroxaban cost less and resulted in more QALYs compared with warfarin in the treatment of VTE.

Stevanovic et al. 2016 (114)
A Markov model conducted from a societal perspective in Netherlands setting. The analysis suggested that dabigatran is cost-effective or even cost-saving compared with VKAs for the treatment of VTE.

Regulatory information

12. Summary of regulatory status and market availability of the medicine.

Dabigatran, Rivaroxaban, Apixaban and Edoxaban are widely available in most of the clinical settings. On the following table, we summarized their regulatory status.
<table>
<thead>
<tr>
<th>Non-valvular Atrial Fibrillation</th>
<th>Administration</th>
<th>Agency</th>
<th>and Medical Devices Agency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong></td>
<td>Approved</td>
<td>Approved</td>
<td>Approved</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>Approved</td>
<td>Approved</td>
<td>Approved</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td>Approved</td>
<td>Approved</td>
<td>Approved</td>
</tr>
<tr>
<td><strong>Edoxaban</strong></td>
<td>Approved</td>
<td>Approved</td>
<td>Approved</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Venous thromboembolism</th>
<th>Administration</th>
<th>Agency</th>
<th>and Medical Devices Agency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong></td>
<td>Approved</td>
<td>Approved</td>
<td>Approved</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>Approved</td>
<td>Approved</td>
<td>Approved</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td>Approved</td>
<td>Approved</td>
<td>Approved</td>
</tr>
<tr>
<td><strong>Edoxaban</strong></td>
<td>Approved</td>
<td>Approved</td>
<td>Approved</td>
</tr>
</tbody>
</table>

13. Availability of pharmacopoeial standards

**Dabigatran**
- International Pharmacopoeia: No
- British Pharmacopoeia: No
- European Pharmacopoeia: No
- United States Pharmacopoeia: No

**Rivaroxaban**
- International Pharmacopoeia: No
- British Pharmacopoeia: No
- European Pharmacopoeia: No
- United States Pharmacopoeia: No

**Apixaban**
- International Pharmacopoeia: No
- British Pharmacopoeia: No
European Pharmacopoeia: No

United States Pharmacopoeia: No

**Edoxaban**

International Pharmacopoeia: No

British Pharmacopoeia: No

European Pharmacopoeia: No

United States Pharmacopoeia: No

**References**


50. Canadian Agency for D, Technologies in H. Rivaroxaban (Xarelto): Treatment of Venous Thromboembolic Events (Deep Vein Thrombosis [DVT], Pulmonary Embolism [PE]) and Prevention of Recurrent DVT and PE2015 2015/08/None.


Appendix 1 – Evidence to Decision Framework: DOAC vs VKA for individuals with non-valvular atrial fibrillation

### Problem
Is the problem a priority?

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Probably no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>● Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Varies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Don’t know</td>
<td></td>
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</tr>
</tbody>
</table>

Non-valvular atrial fibrillation is the most common cardiac arrhythmia. The number of individuals with atrial fibrillation has been estimated in 33.5 million worldwide (7).

Without antithrombotic treatment, the risk of stroke in patients with atrial fibrillation is around 5% per year, but it can be as high as 10% per year if other risk factors are present (8). In a cohort of 15,400 individuals with atrial fibrillation in 47 countries, the highest number of strokes occurred in patients in Africa (incidence 89/1137 [8%] per year), China (incidence 143/2023 [7%] per year), and Southeast Asia (incidence 88/1331 [7%] per year) (9).

In low and middle-income countries, stroke is associated with an increased mortality and significant disability, specially, in disadvantaged populations (10-12). Additionally, according to a recent WHO survey of 177 countries, provisions for the treatment and rehabilitation of patients with stroke are available in less than a quarter of public healthcare facilities in low and middle-income countries (13).

### Desirable Effects
How substantial are the desirable anticipated effects?

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Trivial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>● Small</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Large</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Varies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Don’t know</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th># of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Risk with VKA</td>
<td>Risk difference with DOAC</td>
</tr>
<tr>
<td>Mortality</td>
<td>73641 (13 RCTs)</td>
<td>★★★★ HIGH</td>
<td>RR 0.90 (0.85 to 0.94)</td>
<td>Study population 75 per 1,000</td>
</tr>
<tr>
<td>Stroke</td>
<td>75543 (13 RCTs)</td>
<td>★★★★ HIGHa</td>
<td>RR 0.83 (0.72 to 0.96)</td>
<td>Study population 33 per 1,000</td>
</tr>
<tr>
<td>Systemic Embolism</td>
<td>75018 (13 RCTs)</td>
<td>★★★☆ MODERATEb,c</td>
<td>RR 0.74 (0.48 to 1.13)</td>
<td>Study population 3 per 1,000</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>75480 (13 RCTs)</td>
<td>★★★☆ MODERATEd</td>
<td>RR 0.81 (0.66 to 0.98)</td>
<td>Study population 59 per 1,000</td>
</tr>
</tbody>
</table>
Some heterogeneity was detected ($I^2=47\%$). We did not downgrade by inconsistency.

Some heterogeneity was detected ($I^2=31\%$). We did not downgrade by inconsistency.

The confidence interval probably crosses decision thresholds, therefore do not exclude potential benefit or harm relevant for patients.

Significant heterogeneity was detected ($I^2=77\%$).

### Undesirable Effects

**How substantial are the undesirable anticipated effects?**

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Large</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Small</td>
<td></td>
<td></td>
</tr>
<tr>
<td>● Trivial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Varies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Don’t know</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Certainty of evidence

**What is the overall certainty of the evidence of effects?**

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Very low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>● Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ No included studies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Importance</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>CRITICAL</td>
<td>★★★★★ HIGH</td>
</tr>
<tr>
<td>Stroke</td>
<td>CRITICAL</td>
<td>★★★★★ HIGH</td>
</tr>
<tr>
<td>Systemic Embolism</td>
<td>CRITICAL</td>
<td>★★★★ MODERATE</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>CRITICAL</td>
<td>★★★★ MODERATE</td>
</tr>
</tbody>
</table>

a. Some heterogeneity was detected ($I^2=47\%$). We did not downgrade by inconsistency.

b. Some heterogeneity was detected ($I^2=31\%$). We did not downgrade by inconsistency.

c. The confidence interval probably crosses decision thresholds, therefore do not exclude potential benefit or harm relevant for patients.

d. Significant heterogeneity was detected ($I^2=77\%$).
## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Important uncertainty or variability</td>
<td>In general, stroke is associated with significant disability and with a low health utility. A systematic review of studies evaluating patients’ values and preferences suggested that a reasonable trade-off to assume between stroke and bleeds would be a ratio of disutility in the range of 2:1 to 3:1 (CHEST 2012; 141(2)(Suppl):e1S–e23S)</td>
<td></td>
</tr>
<tr>
<td>● Possibly important uncertainty or variability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Probably no important uncertainty or variability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o No important uncertainty or variability</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Favors the comparison</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Probably favors the comparison</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Does not favor either the intervention or the comparison</td>
<td></td>
<td></td>
</tr>
<tr>
<td>● Probably favors the intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Favors the intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Varies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Don’t know</td>
<td></td>
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</tbody>
</table>

## Resources required

How large are the resource requirements (costs)?

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Large costs</td>
<td>North America:</td>
<td></td>
</tr>
<tr>
<td>o Moderate costs</td>
<td><em>US and Canada:</em> (5) Dabigatran: $300.44–600.88 USD per month Rivaroxaban: $300.42–600.84 USD per month Apixaban: $300.44–600.88 USD per month</td>
<td></td>
</tr>
<tr>
<td>o Negligible costs and savings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Moderate savings</td>
<td><strong>Latin America:</strong></td>
<td></td>
</tr>
<tr>
<td>o Large savings</td>
<td><em>Argentina:</em> (6) Dabigatran: $1,602 Argentine Pesos per month (approximately 50 USD per month) Rivaroxaban: $5,382 Argentine Pesos per month (approximately 150 USD per month) Brazil: (6) Dabigatran: $68.1 Reales per month (approximately 20 USD per month) Rivaroxaban: $68.1 Reales per month (approximately 20 USD per month) Chile: (6)</td>
<td></td>
</tr>
<tr>
<td>● Varies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Don’t know</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td>Dabigatran Cost (Colombian Pesos)</td>
<td>Dabigatran Cost (USD)</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Chile</td>
<td>$ 95,520</td>
<td>$ 30</td>
</tr>
<tr>
<td>Colombia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>$ 68.8 per month</td>
<td>$ 90</td>
</tr>
<tr>
<td>Oceania</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>$ 88.62 Australian Dollars</td>
<td>$ 65</td>
</tr>
</tbody>
</table>

**Cost effectiveness**

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favors the comparison</td>
<td>We identified 2 systematic reviews:</td>
<td></td>
</tr>
<tr>
<td>Probably favors the comparison</td>
<td>The first review included 18 primary studies conducted in North America and Europe. All but one used a Markov model to extrapolate long-term data basing the calculation on the effectiveness and safety results from landmark trials. The majority of the models used the perspective of the payer. Thirteen models compared dabigatran versus warfarin, four rivaroxaban versus warfarin and four apixaban versus warfarin. Although there was some inconsistency among the conclusions of the individual models, the large majority showed that DOACs were cost-effective with ICERs below the willingness to pay thresholds and sometimes dominant over warfarin (95).</td>
<td></td>
</tr>
<tr>
<td>Does not favor either the</td>
<td>The second review identified 26 primary studies evaluating apixaban versus warfarin conducted in North America, Latin America and Europe. All the studies except of one used a Markov model to extrapolate long-term data with the effectiveness and safety results from landmark trials. The majority of the models used the perspective of the payer with a lifetime horizon. The results showed that apixaban was cost-effective with ICERs below the willingness to pay thresholds (96).</td>
<td></td>
</tr>
<tr>
<td>intervention or the comparison</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probably favors the intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favors the intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No included studies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Equity
**What would be the impact on health equity?**

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced</td>
<td>In real life practice, a large proportion of community care patients have poorly controlled anticoagulation with vitamin K antagonists. In one study in Europe, the proportion of patients with poorly controlled treatment varied from 34.6% in the United Kingdom to 55.8% in Germany (19). The situation in low and middle income-countries is probably worst, as showed by a prospective cohort of patients with newly diagnosed atrial fibrillation, in whom the proportion of individuals with poor control reached 78% and 83% in Latin America and Asia compared with approximately 50% in North America and Europe (20). As can be expected, poor anticoagulation is associated with worst outcomes. In the study by Hass et al, poor anticoagulation control was associated with an increased risk of stroke (HR 2.55, 95% CI 1.61 to 4.03), an increased risk of bleeding (HR 1.54, 95% CI 1.04 to 2.26) and a higher mortality (HR 2.39, 95% CI 1.87 to 3.06) (20). Additionally, as suggested by a systematic review of strategies to improve stroke care, in low and middle-income countries an important proportion of patients not have access to regular follow-up and monitoring of the dose of vitamin K antagonists, which make physicians reluctant to start anticoagulation in patients who would benefit otherwise (21). Finally, a recent observational study evaluating prescription patterns in individual with atrial fibrillation in the US suggested that the probability of receiving DOAC instead of vitamin K antagonists is higher in educated individuals (OR 1.43, 95% CI 1.31–1.56) and with high income (OR 1.36, 95% CI 1.27–1.45) (22). This pattern is probably even more accentuated in low and middle-income countries, although only anecdotal evidence was identified.</td>
<td></td>
</tr>
<tr>
<td>Probably reduced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probably no impact</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probably increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Don't know</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Acceptability
**Is the intervention acceptable to key stakeholders?**

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td><strong>DOAC are associated with higher satisfaction but similar adherence in comparison to VKA. Half of patients on VKA would switch to DOAC</strong></td>
<td></td>
</tr>
<tr>
<td>Probably no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probably yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Don't know</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Observational research suggests the following acceptability and barriers associated with DOAC treatment in VTE patients:

**DOAC satisfaction:** VTE patient satisfaction with DOAC is higher and treatment burden lower than with LMWH/VKA (Bamber et al., 2013)(Attaya
**Adherence DOAC vs. VKA:** medication adherence is similar in patients using DOAC or VKA. (Castellucci et al., 2015)

**Switching from VKA to DOAC:** half of VKA patients are willing to switch to DOAC, with men and older patients being more willing to switch than their counterparts. (Attaya et al., 2012)

<table>
<thead>
<tr>
<th>Feasibility</th>
<th>Is the intervention feasible to implement?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>JUDGEMENT</strong></td>
<td><strong>RESEARCH EVIDENCE</strong></td>
</tr>
<tr>
<td>○ No</td>
<td>○ Yes</td>
</tr>
<tr>
<td>○ Probably no</td>
<td>○ Probably yes</td>
</tr>
<tr>
<td>○ Probably yes</td>
<td></td>
</tr>
</tbody>
</table>

DOACs are easier to initiate since do not require injections (in most cases) and INR titration. Also, they are generally available in most settings.
Appendix 2 – Evidence to Decision Framework: DOAC vs VKA for individuals with venous thromboembolism

**Problem**

*Is the problem a priority?*

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Probably no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Probably yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>● Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Varies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Don’t know</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Deep Venous Thrombosis and Pulmonary Embolism are major contributors to global disease burden. Their estimate incidence ranges from 0.7 to 2.7 per 1000 patients-year in Western Europe, 1.1 to 2.4 per 1000 patients-year in North America and 0.2 to 1.6 patients-year in Latin America and Asia (14). Additionally, venous thromboembolism markedly increases with age, with incidences as high as 4.29 to 5.64 per 1000 patients-year in individuals older than 70 years (15, 16). Thus, venous thromboembolism is like to become an even more prominent problem with population aging.

**Desirable Effects**

*How substantial are the desirable anticipated effects?*

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Trivial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>● Small</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Large</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Varies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Don’t know</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Nr of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects’ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>28778 (12 RCTs)</td>
<td>⬤️ ⬤️ ⬤️ Moderate</td>
<td>RR 0.99 (0.85 to 1.15)</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>39 per 1,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0 fewer per 1,000 (6 fewer to 6 more)</td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td>28571 (12 RCTs)</td>
<td>⬤️ ⬤️ ⬤️ Moderate</td>
<td>RR 0.97 (0.77 to 1.23)</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20 per 1,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 fewer per 1,000 (5 fewer to 5 more)</td>
</tr>
<tr>
<td>Proximal Deep Venous Thrombosis</td>
<td>28668 (12 RCTs)</td>
<td>⬤️ ⬤️ Moderate</td>
<td>RR 0.80 (0.59 to 1.09)</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>26 per 1,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 fewer per 1,000 (11 fewer to 2 more)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>28876 (12 RCTs)</td>
<td>⬤️ ⬤️ ⬤️ High</td>
<td>RR 0.63 (0.47 to 0.84)</td>
<td>Study population</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17 per 1,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 fewer per 1,000 (9 fewer to 3 fewer)</td>
</tr>
</tbody>
</table>

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>Confidence interval around absolute estimates are wide and do not rule out potential benefit or harm important to patients</td>
</tr>
<tr>
<td>b.</td>
<td>Some heterogeneity was observed I²=31%, however we did not rate down by inconsistency</td>
</tr>
<tr>
<td>c.</td>
<td>A systematic review of 13 prospective cohort studies and 56 randomized trials showed a risk of bleeding of 2.1% in patients treated for 6 months with anticoagulants (Ann Intern Med. 2010;152:578-589). This risk was used as “high risk population”</td>
</tr>
</tbody>
</table>
### Undesirable Effects

How substantial are the undesirable anticipated effects?

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Large</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Small</td>
<td></td>
<td></td>
</tr>
<tr>
<td>● Trivial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Varies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Don’t know</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Certainty of evidence

What is the overall certainty of the evidence of effects?

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Very low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>● Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ No included studies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Importance</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>CRITICAL</td>
<td>⨁⨁⨁◯                    MODERATE&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td>CRITICAL</td>
<td>⨁⨁⨁◯                    MODERATE&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Proximal Deep Venous Thrombosis</td>
<td>CRITICAL</td>
<td>⨁⨁⨁◯                    MODERATE&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>CRITICAL</td>
<td>⨁⨁⨁⨁                  HIGH&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

- a. Confidence interval around absolute estimates are wide and do not rule out potential benefit or harm important to patients
- b. Some heterogeneity was observed I²=31%, however we did not rate down by inconsistency
## Values
Is there important uncertainty about or variability in how much people value the main outcomes?

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
</table>
| ○ Important uncertainty or variability  ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability | The relative importance of the outcomes is as follows:  
Pulmonary embolism: 0.63-0.93 (different methods)  
Deep vein thrombosis: 0.64-0.99 (different methods)  
Deep vein thrombosis patients' own current health: 0.95 (Time trade off)  
Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off)  
Minor intracranial bleeding event: 0.75 (standard gamble)  
Major intracranial bleeding event: 0.15 (standard gamble)  
Central nervous system bleeding: 0.29-0.60 (standard gamble) | |

## Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison  ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don’t know</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


## Resources required

**How large are the resource requirements (costs)?**

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
</table>
| ○ Large costs  
○ Moderate costs  
○ Negligible costs and savings  
○ Moderate savings  
○ Large savings  
● Varies  
○ Don’t know | **North America:**  
US and Canada: (5)  
Dabigatran: $ 300.44–600.88 USD per month  
Rivaroxaban: $ 300.42–600.84 USD per month  
Apixaban: $ 300.44–600.88 USD per month | |
| | **Latin America:**  
Argentina: (6)  
Dabigatran: $ 1,602 Argentine Pesos per month (approximately 50 USD per month)  
Rivaroxaban: $ 5,382 Argentine Pesos per month (approximately 150 USD per month)  
Brazil: (6)  
Dabigatran: $ 68.1 Reales per month (approximately 20 USD per month)  
Rivaroxaban: $ 68.1 Reales per month (approximately 20 USD per month)  
Chile: (6)  
Dabigatran: $ 19,500 Chilean Pesos per month (approximately 30 USD per month)  
Rivaroxaban: $ 44,040 Chilean Pesos per month (approximately 65 USD per month)  
Colombia: (6)  
Dabigatran: $ 95,520 Colombian Pesos per month (approximately 30 USD per month)  
Rivaroxaban: $ 208,500 Colombian Pesos per month (approximately 65 USD per month) | |
| | **Europe:**  
UK: (93)  
Dabigatran: $ £68.8 per month (approximately 90 USD per month)  
Rivaroxaban: $ £68.8 per month (approximately 90 USD per month)  
Apixaban: $ £68.8 per month (approximately 90 USD per month)  
Edoxaban: $ £68.8 per month (approximately 90 USD per month) | |
| | **Oceania:**  
Australia: (94)  
Dabigatran: $ 88.62 Australian Dollars per month (approximately 65 USD per month)  
Rivaroxaban: $ 87.41 Australian Dollars per month (approximately 60 USD per month)  
Apixaban: $ 93.16 Australian Dollars per month (approximately 68 USD per month) | |

## Cost effectiveness

**Does the cost-effectiveness of the intervention favor the intervention or the comparison?**

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
</table>
| ○ Favors the comparison  
○ Probably favors the comparison  
○ Does not favor either the intervention or the comparison  
● Probably favors the intervention  
○ Favors the intervention  
○ Varies  
○ No included studies | Five economic analyses reported the cost comparisons between using DOACs and LMWH/VKA for treatment of VTE. All these reports suggest **DOAC use is cost-saving compared with warfarin.** Except one of them using hypothetical health plan population, the other four analyses were on real world data.  
Fifteen economic analyses compared the cost and effectiveness of DOACs versus VKA on the treatment of VTE. All of them suggest **DOACs as cost-effective alternative to LMWH or VKA.** The studied DOACs mainly include apixaban and rivaroxaban. | |
## Equity

### What would be the impact on health equity?

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced</td>
<td>Reduced</td>
<td></td>
</tr>
<tr>
<td>Probably reduced</td>
<td>Probably reduced</td>
<td></td>
</tr>
<tr>
<td>Probably no impact</td>
<td>Probably no impact</td>
<td></td>
</tr>
<tr>
<td>Probably increased</td>
<td>Probably increased</td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Varies</td>
<td>Varies</td>
<td></td>
</tr>
<tr>
<td>Don’t know</td>
<td>Don’t know</td>
<td></td>
</tr>
</tbody>
</table>

In real life practice, a large proportion of community care patients have poorly controlled anticoagulation with vitamin K antagonists. In one study in Europe, the proportion of patients with poorly controlled treatment varied from 34.6% in the United Kingdom to 55.8% in Germany (19). The situation in low and middle income-countries is probably worst, as showed by a prospective cohort of patients with newly diagnosed atrial fibrillation, in whom the proportion of individuals with poor control reached 78% and 83% in Latin America and Asia compared with approximately 50% in North America and Europe (20).

As can be expected, poor anticoagulation is associated with worst outcomes. In the study by Hass et al, poor anticoagulation control was associated with an increased risk of stroke (HR 2.55, 95% CI 1.61 to 4.03), an increased risk of bleeding (HR 1.54, 95% CI 1.04 to 2.26) and a higher mortality (HR 2.39, 95% CI 1.87 to 3.06) (20).

Additionally, as suggested by a systematic review of strategies to improve stroke care, in low and middle-income countries an important proportion of patients not have access to regular follow-up and monitoring of the dose of vitamin K antagonists, which make physicians reluctant to start anticoagulation in patients who would benefit otherwise (21).

Finally, a recent observational study evaluating prescription patterns in individual with atrial fibrillation in the US suggested that the probability of receiving DOAC instead of vitamin K antagonists is higher in educated individuals (OR 1.43, 95% CI 1.31–1.56) and with high income (OR 1.36, 95% CI 1.27–1.45) (22). This pattern is probably even more accentuated in low and middle-income countries, although only anecdotal evidence was identified.

## Acceptability

### Is the intervention acceptable to key stakeholders?

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<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>DOAC are associated with higher satisfaction but similar adherence in comparison to VKA. Half of patients on VKA would switch to DOAC</td>
<td></td>
</tr>
<tr>
<td>Probably no</td>
<td>Observational research suggests the following acceptability and barriers associated with DOAC treatment in VTE patients:</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>DOAC satisfaction: VTE patient satisfaction with DOAC is higher and treatment burden lower than with LMWH/VKA (Bamber et al., 2013)(Attaya et al., 2012)</td>
<td></td>
</tr>
<tr>
<td>Varies</td>
<td>Adherence DOAC vs. VKA: medication adherence is similar in patients using DOAC or VKA. (Castellucci et al., 2015)</td>
<td></td>
</tr>
<tr>
<td>Don’t know</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Switching from VKA to DOAC: half of VKA patients are willing to switch to DOAC, with men and older patients being more willing to switch than their counterparts. (Attaya et al., 2012)

<table>
<thead>
<tr>
<th>Feasibility</th>
<th>Is the intervention feasible to implement?</th>
</tr>
</thead>
<tbody>
<tr>
<td>JUDGEMENT</td>
<td>RESEARCH EVIDENCE</td>
</tr>
<tr>
<td>● Yes</td>
<td>DOACs are easier to initiate since do not require injections (in most cases) and INR titration. Also, they are generally available in most settings</td>
</tr>
<tr>
<td>○ No</td>
<td></td>
</tr>
<tr>
<td>○ Probably no</td>
<td></td>
</tr>
<tr>
<td>○ Probably yes</td>
<td></td>
</tr>
<tr>
<td>● Yes</td>
<td></td>
</tr>
<tr>
<td>○ Varies</td>
<td></td>
</tr>
<tr>
<td>○ Don’t know</td>
<td></td>
</tr>
</tbody>
</table>
## Appendix 3 – Forest Plots: DOAC vs VKA for individuals with non-valvular atrial fibrillation

### Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Total Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.1.1 Dabigatran</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01136468</td>
<td>0</td>
<td>104</td>
<td>62</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>PROACT</td>
<td>0</td>
<td>169</td>
<td>70</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>RE-LY</td>
<td>884 (95% CI)</td>
<td>12091</td>
<td>487</td>
<td>6022</td>
<td>24.1%</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>12364</td>
<td>6154</td>
<td>24.1%</td>
<td>0.90 [0.81, 1.01]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>884</td>
<td>12091</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable

Test for overall effect: Z = 1.86 (P = 0.06)

| **1.1.2 Rivaroxaban** |                     |                |              |                                |                                |
| J-ROCKET AF 2012     | 7                   | 617            | 5            | 627                            | 0.2%                           |
| NCT00973126           | 0                   | 75             | 0            | 27                             | Not estimable                  |
| NCT00973128           | 0                   | 50             | 0            | 25                             | Not estimable                  |
| ROCKET AF 2011       | 208 (95% CI)        | 7961           | 250          | 7082                           | 8.3%                           |
| **Subtotal (95% CI)** | 7823                | 7772           | 8.3%         | 0.81 [0.70, 1.00]               |                                |
| **Total events**     | 215                 | 7961           |              |                                |                                |

Heterogeneity: Tau² = 0.00, CH² = 0.77, df = 1 (P = 0.38), I² = 0%

Test for overall effect: Z = 1.85 (P = 0.06)

| **1.1.3 Apixaban** |                     |                |              |                                |                                |
| ABT-393 Continuation 2011 | 603         | 9120           | 669          | 9081                           | 24.2%                          |
| ABT-393 Continuation 2011 | 0            | 148            | 0            | 74                             | Not estimable                  |
| **Subtotal (95% CI)** | 9268              | 9135           | 24.2%        | 0.90 [0.81, 1.00]               |                                |
| **Total events**     | 603                | 9120           |              |                                |                                |

Heterogeneity: Not applicable

Test for overall effect: Z = 2.00 (P = 0.05)

| **1.1.4 Edoxaban** |                     |                |              |                                |                                |
| Edoxaban Asia 2010   | 0                   | 0              | 0            | 0                              | Not estimable                  |
| Edoxaban US/Europe 2010 | 0          | 0              | 0            | 0                              | Not estimable                  |
| ENGAGE AF-TIMI 48 2013 | 1510       | 14069          | 839          | 7036                           | 43.2%                          |
| **Total events**     | 14069              | 839            |              | 0.90 [0.83, 0.97]               |                                |

Heterogeneity: Not estimable

Test for overall effect: Z = 3.60 (P = 0.0091)

| **Total (95% CI)** | 43524              | 30117          | 100.0%       | 0.90 [0.85, 0.94]               |                                |
| **Total events**   | 32122              | 2250           |              |                                |                                |

Heterogeneity: Tau² = 0.00, CH² = 1.22, df = 4 (P = 0.877), I² = 0%

Test for overall effect: Z = 4.14 (P < 0.0001)

Test for subgroup differences: CH² = 0.45, df = 3 (P = 0.93), I² = 0%
### Stroke

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>1.2.1 Dabigatran</td>
<td></td>
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<tr>
<td>NCT011364468</td>
<td>0</td>
<td>104</td>
<td>0</td>
<td>Not estimable</td>
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<tr>
<td>PETRO</td>
<td>0</td>
<td>169</td>
<td>0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>RE-LV</td>
<td>293</td>
<td>12991</td>
<td>185</td>
<td>0.28 (0.20, 0.38)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>12364</td>
<td>6032</td>
<td>22.9%</td>
<td>0.79 (0.66, 0.95)</td>
</tr>
<tr>
<td>Total events</td>
<td>293</td>
<td>185</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Heterogeneity: Not applicable</td>
</tr>
</tbody>
</table>

#### 1.2.2 Rivaroxaban

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<thead>
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<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>J-ROCKET AF 2012</td>
<td>10</td>
<td>617</td>
<td>21</td>
<td>0.48 (0.23, 1.00)</td>
</tr>
<tr>
<td>NCT0097524-05</td>
<td>0</td>
<td>75</td>
<td>0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>NCT00973323</td>
<td>0</td>
<td>50</td>
<td>0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>ROCKET AF 2011</td>
<td>184</td>
<td>7961</td>
<td>221</td>
<td>0.84 (0.69, 1.01)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>7823</td>
<td>7772</td>
<td>25.3%</td>
<td>0.71 (0.45, 1.11)</td>
</tr>
<tr>
<td>Total events</td>
<td>194</td>
<td>242</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Heterogeneity: Tau² = 0.00, CI² = 2.05, df = 1 (P = 0.15), I² = 51%</td>
</tr>
</tbody>
</table>

#### 1.2.3 Apixaban

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE 2011</td>
<td>139</td>
<td>9120</td>
<td>250</td>
<td>0.79 (0.66, 0.95)</td>
</tr>
<tr>
<td>ARISTOTLE-J 2011</td>
<td>0</td>
<td>188</td>
<td>2</td>
<td>0.97 (0.80, 1.17)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>9268</td>
<td>9155</td>
<td>22.2%</td>
<td>0.38 (0.15, 0.83)</td>
</tr>
<tr>
<td>Total events</td>
<td>139</td>
<td>253</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Heterogeneity: Tau² = 1.75, CI² = 2.54, df = 1 (P = 0.11), I² = 61%</td>
</tr>
</tbody>
</table>

#### 1.2.4 Edoxaban

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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<td>Events</td>
<td>Total</td>
<td>Weight</td>
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<tr>
<td>Edoxaban Asia 2010</td>
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<td>259</td>
<td>0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Edoxaban US/Europe 2010</td>
<td>5</td>
<td>885</td>
<td>7</td>
<td>0.47 (0.11, 1.94)</td>
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<tr>
<td>ENGAGE AF-TIMI 48 2011</td>
<td>641</td>
<td>14068</td>
<td>317</td>
<td>0.91 (0.89, 1.15)</td>
</tr>
<tr>
<td>Yamashita 2012</td>
<td>1</td>
<td>396</td>
<td>0</td>
<td>0.98 (0.84, 1.13)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>15517</td>
<td>7490</td>
<td>28.8%</td>
<td>1.00 (0.88, 1.15)</td>
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<tr>
<td>Total events</td>
<td>647</td>
<td>320</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Heterogeneity: Tau² = 0.00, CI² = 1.32, df = 2 (P = 0.57), I² = 0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.83 (0.72, 0.96)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Total events</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Heterogeneity: Tau² = 0.02, CI² = 13.31, df = 7 (P = 0.05), I² = 47%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Test for subgroup differences: CI² = 6.14, df = 3 (P = 0.11), I² = 51.1%</td>
</tr>
</tbody>
</table>
Systemic Embolism

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
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<th>Risk Ratio M-H, Random, 95% CI</th>
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<td>Babigatran</td>
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<td></td>
</tr>
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<td>104</td>
<td>0</td>
<td>62</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PETRO</td>
<td>0</td>
<td>160</td>
<td>0</td>
<td>70</td>
<td>Not estimable</td>
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<td></td>
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<tr>
<td>FE-IV</td>
<td>23</td>
<td>12091</td>
<td>14</td>
<td>6032</td>
<td>24.7%</td>
<td>0.82 [0.42, 1.59]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>12364</td>
<td>8134</td>
<td>24.7%</td>
<td>0.82 [0.42, 1.59]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>23</td>
<td></td>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>Not applicable</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for overall effect Z = 0.59 (P = 0.55)

| Rivaroxaban       |                     |       |                |       |        |                               |                               |
| J-ROCKET AF 2012  | 1                   | 617   | 1              | 627   | 2.3%   | 1.00 [0.66, 1.59]             |                               |
| NCT005732-05      | 0                   | 75    | 0              | 27    | Not estimable |                               |                               |
| NCT00973323       | 0                   | 50    | 0              | 26    | Not estimable |                               |                               |
| ROCKET AF 2011    | 5                   | 7962  | 22             | 7285  | 14.9%  | 0.23 [0.09, 0.60]             |                               |
| Subtotal (95% CI) | 7823                | 7772  | 17.2%          | 0.27 [0.11, 0.67] |                               |                               |
| Total events      | 6                   |       | 23             |       |        |                               |                               |
| Heterogeneity     | Tau² = 0.00, Chi² = 0.98, df = 1 (P = 0.32), I² = 0% | | | | | |

Test for overall effect Z = 2.82 (P = 0.005)

| Apixaban          |                     |       |                |       |        |                               |                               |
| ARISTOTLE 2011    | 15                  | 9120  | 17             | 9081  | 23.4%  | 0.88 [0.44, 1.76]             |                               |
| ARISTOTLE-J 2011  | 0                   | 548   | 0              | 74    | Not estimable |                               |                               |
| Subtotal (95% CI) | 9268                | 9155  | 23.4%          | 0.88 [0.44, 1.76] |                               |                               |
| Total events      | 15                  |       | 17             |       |        |                               |                               |
| Heterogeneity     | Not applicable      |       |                |       |        |                               |                               |

Test for overall effect Z = 0.37 (P = 0.71)

| Edoxaban          |                     |       |                |       |        |                               |                               |
| Edoxaban Asia 2010| 0                   | 259   | 0              | 75    | Not estimable |                               |                               |
| Edoxaban US/Europe| 2                   | 895   | 0              | 250   | 2.0%   | 1.49 [0.67, 2.81]             |                               |
| ENGAGE-AF-TIMI 48| 44                  | 14069 | 23             | 7036  | 32.7%  | 0.96 [0.58, 1.55]             |                               |
| Yamashita 2012    | 0                   | 0     | 0              | 0     | Not estimable |                               |                               |
| Subtotal (95% CI) | 15121               | 7361  | 34.7%          | 0.97 [0.59, 1.59] |                               |                               |
| Total events      | 46                  |       | 23             |       |        |                               |                               |
| Heterogeneity     | Tau² = 0.00, Chi² = 0.06, df = 1 (P = 0.81), I² = 0% | | | | | |

Test for overall effect Z = 0.33 (P = 0.74)

Total (95% CI) 44576 30442 100.0% 0.74 [0.48, 1.13]

Total events 90 77

Heterogeneity Tau² = 0.08, Chi² = 7.20, df = 5 (P = 0.21), I² = 21%

Test for overall effect Z = 1.59 (P = 0.12)

Test for subgroup differences Chi² = 6.08, df = 3 (P = 0.11), I² = 50.6%

Favours DOAC
Favours VKA
## Major Bleeding

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.4.1 Daigobatan</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>NCT011364408</td>
<td>1</td>
<td>104</td>
<td>62</td>
<td>0.5%</td>
<td>0.60 [0.04, 9.36]</td>
</tr>
<tr>
<td>PETRO</td>
<td>0</td>
<td>169</td>
<td>0</td>
<td>70</td>
<td>Not estimable</td>
</tr>
<tr>
<td>FE-IV</td>
<td>697</td>
<td>12091</td>
<td>397</td>
<td>8032</td>
<td>22.4%</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>12384</td>
<td>6134</td>
<td>24.8%</td>
<td>0.87 [0.76, 0.98]</td>
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</tr>
<tr>
<td><strong>Total events</strong></td>
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<td>1398</td>
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<tr>
<td><strong>Heterogeneity</strong></td>
<td>Tau² = 0.00, Chi² = 0.07, df = 1 (P = 0.79), I² = 0%</td>
<td>Test for overall effect Z = 2.22 (P = 0.03)</td>
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</tr>
</tbody>
</table>

| **1.4.2 Rivarexaban** |                     |              |        |                                |                                |
| j-ROCKET AF 2012    | 26                  | 629          | 30     | 639                            | 8.9%                           |
| NCT00973245         | 0                   | 75           | 0      | 27                             | Not estimable                   |
| **ROCKET AF 2011**  | 395                 | 7111         | 386    | 7125                           | 21.8%                          |
| **Subtotal (95% CI)** | 7875               | 7817         | 30.7%  | 1.01 [0.89, 1.16]               |
| **Total events**    | 421                | 416          |        |                                |                                |
| **Heterogeneity**   | Tau² = 0.00, Chi² = 0.28, df = 1 (P = 0.54), I² = 0% | Test for overall effect Z = 0.21 (P = 0.84) |

| **1.4.3 Apixaban** |                     |              |        |                                |                                |
| ARISTOTLE 2011      | 327                 | 9088         | 462    | 9052                           | 21.7%                          |
| ARISTOTLE-J 2011    | 0                   | 141          | 1      | 25                            | 0.4%                           |
| **Subtotal (95% CI)** | 9231               | 9127         | 22.1%  | 0.70 [0.61, 0.81]               |
| **Total events**    | 327                | 463          |        |                                |                                |
| **Heterogeneity**   | Tau² = 0.00, Chi² = 0.73, df = 1 (P = 0.39), I² = 0% | Test for overall effect Z = 4.90 (P < 0.0001) |

| **1.4.4 Edoxaban** |                     |              |        |                                |                                |
| Edoxaban Asia 2019  | 0                   | 359          | 2      | 75                             | 0.4%                           |
| Edoxaban US/Europe 2010 | 12             | 903          | 1      | 250                            | 0.8%                           |
| ENGAGE AF-TIMI 48 2013 | 672           | 12614        | 524    | 7012                           | 22.6%                          |
| Yamasaki 2012       | 5                   | 394          | 0      | 125                            | 0.4%                           |
| **Subtotal (95% CI)** | 15460             | 7462         | 24.3%  | 0.90 [0.27, 2.93]               |
| **Total events**    | 689                | 527          |        |                                |                                |
| **Heterogeneity**   | Tau² = 0.67, Chi² = 5.41, df = 3 (P = 0.14), I² = 44% | Test for overall effect Z = 0.10 (P = 0.86) |

| **Total (95% CI)**  | 44930              | 30580        | 100.0% | 0.81 [0.66, 0.98]               |
| **Total events**    | 2135               | 1804         |        |                                |                                |
| **Heterogeneity**   | Tau² = 0.04, Chi² = 38.86, df = 9 (P < 0.0001), I² = 77% | Test for overall effect Z = 2.20 (P = 0.03) |
| **Test for subgroup differences** | Chi² = 14.50, df = 3 (P = 0.003), I² = 78.9% | |

Harms: |

- **Favours DOAC** |
- **Favours VKA**
# Appendix 4 – Forest Plots: DOAC vs VKA for individuals with venous thromboembolism

## Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Total</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.1.1 Dabigatran</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-COVER</td>
<td>21</td>
<td>1274</td>
<td>1295</td>
<td>6.3%  0.99 [0.65, 1.51]</td>
</tr>
<tr>
<td>RE-COVER II</td>
<td>25</td>
<td>1279</td>
<td>1294</td>
<td>7.6%  1.01 [0.58, 1.74]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>2553</strong></td>
<td><strong>2554</strong></td>
<td><strong>5107</strong></td>
<td><strong>13.9%  1.00 [0.67, 1.50]</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>46</strong></td>
<td><strong>46</strong></td>
<td><strong>92</strong></td>
<td><strong>46</strong> [1.00]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; CHI² = 0.00; df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)

| **1.1.2 Rivaroxaban** |              |         |       |                                |
| EINSTEIN-DVT study   | 24           | 405     | 429   | 2.3%  0.95 [0.35, 2.58]         |
| EINSTEIN-PE study    | 38           | 1718    | 1756  | 13.6% 0.77 [0.51, 1.17]         |
| J-EINSTEIN study     | 58           | 2412    | 2470  | 16.3% 1.16 [0.80, 1.68]         |
| ODYSSEY-DVT study    | 12           | 478     | 590   | 0.6%  3.05 [0.40, 23.04]         |
| **Subtotal (95% CI)** | **5091**     | **4384** | **9475** | **32.4%  0.99 [0.76, 1.29]** |
| **Total events**     | **126**      | **105** | **331** | **126** [0.94]                 |

Heterogeneity: Tau² = 0.00; CHI² = 3.37; df = 4 (P = 0.50); I² = 0%
Test for overall effect: Z = 0.08 (P = 0.94)

| **1.1.3 Apixaban** |              |         |       |                                |
| AMPHIBY study       | 41           | 2676    | 3117  | 13.3% 0.79 [0.53, 1.19]         |
| AMPHIBY-I           | 0            | 40      | 40    | Not estimable                   |
| Botticelli DVT study| 5            | 385     | 440   | 0.3%  3.62 [0.20, 65.00]         |
| **Subtotal (95% CI)** | **3101**     | **2855** | **5956** | **14.1%  0.85 [0.46, 1.55]** |
| **Total events**    | **46**       | **52**  | **98** | **46** [0.59]                   |

Heterogeneity: Tau² = 0.06; CHI² = 1.05; df = 1 (P = 0.31); I² = 5%
Test for overall effect: Z = 0.54 (P = 0.59)

| **1.1.4 Edoxaban** |              |         |       |                                |
| HELIX-US study      | 132          | 4118    | 4250  | 39.5% 1.05 [0.82, 1.33]         |
| PIAGIA 2014         | 0            | 0       | 0     | Not estimable                   |
| **Subtotal (95% CI)** | **4118**     | **4222** | **8340** | **39.3%  1.05 [0.82, 1.33]** |
| **Total events**    | **132**      | **126** | **258** | **126** [0.70]                 |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.70)

| **Total (95% CI)** |              |         |       |                                |
|-------------------|--------------|---------|-------|                                |
| **14863**         | **13915**    | **28778** | **100.0%** | **0.99 [0.85, 1.15]** |
| **Total events**  | **250**      | **229** | **479** | **229** [1.00]                 |

Heterogeneity: Tau² = 0.00; CHI² = 5.52; df = 9 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.17 (P = 0.86)
Test for subgroup differences: CHI² = 0.44; df = 3 (P = 0.93); I² = 0%
## Pulmonary Embolism

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Total Events</th>
<th>Control Events</th>
<th>Total Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-COVER</td>
<td>12</td>
<td>1274</td>
<td>7</td>
<td>1265</td>
<td>6.5%</td>
<td>1.84 [0.74, 4.63]</td>
</tr>
<tr>
<td>RE-COVER II</td>
<td>7</td>
<td>1279</td>
<td>13</td>
<td>1289</td>
<td>6.5%</td>
<td>0.54 [0.22, 1.36]</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>2553</td>
<td>2554</td>
<td>20</td>
<td>23</td>
<td>13.0%</td>
<td>1.00 [0.30, 3.32]</td>
</tr>
<tr>
<td>Total events</td>
<td>20</td>
<td>20</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Heterogeneity Tau² = 0.51; Chi² = 3.43, df = 1 (P = 0.06); I² = 71%</td>
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<tr>
<td>Test for overall effect: Z = 0.00 (P = 1.00)</td>
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</tr>
</tbody>
</table>

| **Rivaroxaban**         |                     |              |                |              |                               |                               |
| Einsein–DVT dose study  | 2                   | 348          | 1              | 101          | 1.6%                          | 0.58 [0.05, 6.34]              |
| Einsein–DVT study       | 20                  | 1731         | 18             | 1718         | 13.6%                         | 1.10 [0.59, 2.08]              |
| Einsein–FE study        | 22                  | 2412         | 19             | 2412         | 14.6%                         | 1.16 [0.63, 2.21]              |
| Jr–Einsein study        | 0                   | 0            | 0              | 0            | Not estimable                 |                              |
| Odda–DVT study          | 3                   | 451          | 0              | 112          | 0.6%                          | 1.85 [0.10, 35.19]             |
| Subtotal (95% CI)       | 4929                | 4344         | 38             |              | 29.7%                         | 1.12 [0.75, 1.71]              |
| Total events            | 47                  | 38           |                |              |                               |                               |
| Heterogeneity Tau² = 0.00; Chi² = 0.41, df = 3 (P = 0.94); I² = 0% |
| Test for overall effect: Z = 0.51 (P = 0.61) |

| **Apixaban**            |                     |              |                |              |                               |                               |
| AMPLIFY study           | 27                  | 2691         | 23             | 2704         | 17.8%                         | 1.18 [0.68, 2.05]              |
| AMPLIFY–i              | 0                   | 40           | 1              | 40           | 0.5%                          | 0.33 [0.01, 7.95]              |
| Bartelli DVT study      | 0                   | 358          | 1              | 118          | 0.5%                          | 0.11 [0.00, 5.69]              |
| Subtotal (95% CI)       | 3089                | 2862         | 25             |              | 18.8%                         | 0.76 [0.23, 2.50]              |
| Total events            | 27                  | 25           |                |              |                               |                               |
| Heterogeneity Tau² = 0.40; Chi² = 2.59, df = 2 (P = 0.27); I² = 23% |
| Test for overall effect: Z = 0.45 (P = 0.65) |

| **Edoxaban**            |                     |              |                |              |                               |                               |
| Holmait–VTE study       | 49                  | 4118         | 59             | 4122         | 38.4%                         | 0.83 [0.57, 1.21]              |
| Piazza 2014             | 0                   | 0            | 0              | 0            | Not estimable                 |                              |
| Subtotal (95% CI)       | 4118                | 4122         | 59             |              | 38.4%                         | 0.83 [0.57, 1.21]              |
| Total events            | 49                  | 59           |                |              |                               |                               |
| Heterogeneity Non applicable |
| Test for overall effect: Z = 0.96 (P = 0.34) |

| **Total**               | 14689               | 13882        | 100.0%         | 0.97 [0.77, 1.23] |
| Total events            | 143                 | 142          |                | 0.01 0.1 1 10 100 |

| Favour DOAC Favour VKA  |
### Proximal Deep Venous Thrombosis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Total Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.3.1 Daiabitan</strong></td>
<td></td>
<td></td>
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<tr>
<td>RE-COVER</td>
<td>16</td>
<td>1274</td>
<td>18</td>
<td>1285</td>
<td>12.3%</td>
<td>0.88 [0.45, 1.72]</td>
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<tr>
<td>RE-COVER II</td>
<td>25</td>
<td>1279</td>
<td>17</td>
<td>1289</td>
<td>13.7%</td>
<td>1.48 [0.80, 2.73]</td>
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</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2553</td>
<td></td>
<td>2554</td>
<td></td>
<td>26.0%</td>
<td>1.17 [0.70, 1.93]</td>
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</tr>
<tr>
<td>Total events</td>
<td>41</td>
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<td>35</td>
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<tr>
<td>Heterogeneity Taub = 0.63, Chi² = 1.26, df = 1 (P = 0.26), I² = 20%</td>
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<tr>
<td>Test for overall effect: Z = 0.59 (P = 0.55)</td>
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</tr>
</tbody>
</table>

| **1.3.2 Rivaroxaban** |                     |             |                |             |        |                                 |                                 |
| Estinck-DVT dose study | 4                  | 348         | 7              | 101         | 5.3%   | 0.17 [0.05, 0.56]               |                                 |
| Estinck-DVT study     | 15                  | 1731        | 28             | 1718        | 13.4%  | 0.53 [0.29, 0.99]               |                                 |
| Estinck-FE study      | 10                  | 2412        | 17             | 2401        | 12.5%  | 1.06 [0.55, 2.04]               |                                 |
| J-Study              | 1                   | 78          | 0              | 19          | 0.8%   | 0.71 [0.03, 17.86]              |                                 |
| ODIha-DVT study       | 4                   | 431         | 1              | 112         | 1.8%   | 0.94 [0.12, 7.23]               |                                 |
| Subtotal (95% CI)     | 5007                |             | 4365           |             | 33.9%  | 0.57 [0.29, 1.13]               |                                 |
| Total events          | 52                  |             | 53             |             |        |                                 |                                 |
| Heterogeneity Taub = 0.28, Chi² = 7.54, df = 4 (P = 0.11), I² = 47% |
| Test for overall effect: Z = 1.60 (P = 0.11) |

| **1.3.3 Apixaban**    |                     |             |                |             |        |                                 |                                 |
| AMPERF study          | 20                  | 2691        | 33             | 2704        | 15.2%  | 0.61 [0.35, 1.06]               |                                 |
| AMPERF−                 | 0                   | 40          | 0              | 40          | Not estimable |                                 |                                 |
| Bertoncelli DVT study | 8                   | 358         | 2              | 118         | 3.5%   | 1.52 [0.28, 8.12]               |                                 |
| Subtotal (95% CI)     | 3089                |             | 2862           |             | 18.7%  | 0.67 [0.40, 1.12]               |                                 |
| Total events          | 28                  |             | 35             |             |        |                                 |                                 |
| Heterogeneity Taub = 0.00, Chi² = 0.86, df = 1 (P = 0.35), I² = 0% |
| Test for overall effect: Z = 1.85 (P = 0.06) |

| **1.3.4 Edoxaban** |                     |             |                |             |        |                                 |                                 |
| Hirokami-VTE study   | 57                  | 4118        | 63             | 4122        | 21.4%  | 0.91 [0.63, 1.32]               |                                 |
| Piazza 2014           | 0                   | 0           | 0              | 0           | Not estimable |                                 |                                 |
| Subtotal (95% CI)     | 4118                |             | 4122           |             | 21.4%  | 0.91 [0.63, 1.32]               |                                 |
| Total events          | 57                  |             | 63             |             |        |                                 |                                 |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 0.55 (P = 0.58) |

| Total (95% CI)        | 14767               | 13901       | 100.0%        | 0.80 [0.59, 1.09] |                                 |                                 |
| Total events          | 168                 | 186         |              |              |        |                                 |                                 |
| Heterogeneity Taub = 0.00, Chi² = 14.61, df = 3 (P = 0.001), I² = 58% |
| Test for overall effect: Z = 1.43 (P = 0.15) |

| Test for subgroup differences: Chi² = 3.74, df = 3 (P = 0.29), I² = 19.6% |

Favours DOAC. Favours VKA
### Major Bleeding

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
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<tr>
<td><strong>1.4.1 Dahigaran</strong></td>
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<td></td>
</tr>
<tr>
<td>RE-COVER</td>
<td>20</td>
<td>1274</td>
<td>24</td>
<td>1265</td>
<td>14.2%</td>
<td>0.83 [0.46, 1.49]</td>
<td></td>
</tr>
<tr>
<td>RE-COVER II</td>
<td>15</td>
<td>1279</td>
<td>22</td>
<td>1289</td>
<td>12.6%</td>
<td>0.69 [0.36, 1.32]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>35</td>
<td>2553</td>
<td>46</td>
<td>2534</td>
<td>26.8%</td>
<td>0.76 [0.49, 1.18]</td>
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</tr>
<tr>
<td><strong>Total events</strong></td>
<td>55</td>
<td>5195</td>
<td>74</td>
<td>5121</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity</strong></td>
<td>Tau^2 = 0.06, Chi^2 = 0.17, df = 1 (P = 0.69), I^2 = 0%</td>
<td>Tau^2 = 0.07, Chi^2 = 1.43, df = 1 (P = 0.24), I^2 = 35%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect</strong></td>
<td>Z = 1.22 (P = 0.22)</td>
<td>Z = 1.26 (P = 0.21)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

| **1.4.2 Rivaroxaban** |                     |       |                |       |        |            |            |
| Eisenstein-DVT study | 3                   | 405   | 2              | 137   | 2.5%   | 0.51 [0.09, 3.00] |            |
| Eisenstein-EF study  | 14                  | 1718  | 20             | 1731  | 11.9%  | 0.70 [0.35, 1.38] |            |
| Jr-Eisenstein study  | 0                   | 70    | 0              | 15    |        | Not estimable |            |
| O'Donovon-DVT study  | 10                  | 478   | 0              | 126   | 1.6%   | 5.57 [0.33, 94.38] |            |
| **Subtotal (95% CI)** | 5091               | 4398  | 74             | 4372  | 35.3%  | 0.58 [0.39, 0.88] |            |
| **Total events**  | 55                  | 5195  | 74             | 5121  |        |            |            |
| **Heterogeneity** | Tau^2 = 0.02, Chi^2 = 3.22, df = 3 (P = 0.36), I^2 = 7% | Tau^2 = 3.26, Chi^2 = 16.43, df = 3 (P = 0.001), I^2 = 50% |
| **Test for overall effect** | Z = 2.56 (P = 0.01) | Z = 2.56 (P = 0.01) |            |

| **1.4.3 Apixaban** |                     |       |                |       |        |            |            |
| AMPIFY study       | 15                  | 2676  | 49             | 2680  | 14.6%  | 0.31 [0.17, 0.55] |            |
| AMPIFY II          | 0                   | 40    | 2              | 39    | 0.9%   | 0.20 [0.01, 3.94] |            |
| Durack-DVT study   | 1                   | 385   | 0              | 126   | 1.6%   | 2.50 [0.12, 44.29] |            |
| **Subtotal (95% CI)** | 3101               | 2854  | 51             | 2803  | 16.4%  | 0.33 [0.19, 0.57] |            |
| **Total events**  | 18                  | 5195  | 74             | 5121  |        |            |            |
| **Heterogeneity** | Tau^2 = 0.00, Chi^2 = 1.53, df = 2 (P = 0.40), I^2 = 0% | Tau^2 = 0.00, Chi^2 = 0.00, df = 0 (P = 0.99), I^2 = 0% |
| **Test for overall effect** | Z = 3.96 (P < 0.001) | Z = 3.96 (P < 0.001) |            |

| **1.4.4 Edoxaban** |                     |       |                |       |        |            |            |
| Hokanski-VTE study | 56                  | 4118  | 66             | 4182  | 22.4%  | 0.85 [0.60, 1.23] |            |
| Piazza 2014        | 0                   | 56    | 1              | 29    | 0.8%   | 0.18 [0.01, 4.18] |            |
| **Subtotal (95% CI)** | 4174               | 4151  | 67             | 4118  | 23.3%  | 0.83 [0.59, 1.18] |            |
| **Total events**  | 56                  | 5195  | 74             | 5121  |        |            |            |
| **Heterogeneity** | Tau^2 = 0.00, Chi^2 = 0.94, df = 1 (P = 0.33), I^2 = 0% | Tau^2 = 0.00, Chi^2 = 0.00, df = 0 (P = 0.99), I^2 = 0% |
| **Test for overall effect** | Z = 1.02 (P = 0.31) | Z = 1.02 (P = 0.31) |            |

| **Total (95% CI)** | 14919              | 13957 | 100.0%         | 0.62 [0.47, 0.84] |            |
| **Total events**  | 162                | 238   |                |            |            |
| **Heterogeneity** | Tau^2 = 0.07, Chi^2 = 14.89, df = 10 (P = 0.14), I^2 = 33% | Tau^2 = 0.07, Chi^2 = 14.89, df = 10 (P = 0.14), I^2 = 33% |
| **Test for overall effect** | Z = 3.16 (P = 0.002) | Z = 3.16 (P = 0.002) |
| **Test for subgroup differences** | Chi^2 = 8.64, df = 3 (P = 0.031), I^2 = 65.3% | Chi^2 = 8.64, df = 3 (P = 0.031), I^2 = 65.3% |
|                     |

Favours DOAC. Favours VKA.
Appendix 5 – Search strategy used to identify systematic reviews.

1. dabigatran.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, an, eu, pm, ui]
2. pradaxa.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, an, eu, pm, ui]
3. rivaroxaban.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, an, eu, pm, ui]
4. xarelto.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, an, eu, pm, ui]
5. apixaban.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, an, eu, pm, ui]
6. Eliquis.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, an, eu, pm, ui]
7. Edoxaban.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, an, eu, pm, ui]
8. Lixiana.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, an, eu, pm, ui]
9. Savaysa.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, an, eu, pm, ui]
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. meta-analysis/
12. meta-analysis as topic/
13. (meta analy* or metanaly* or metaanaly*).ti,ab.
14. (reference list* or bibliography* or hand search* or manual search* or relevant journals).ab.
15. ((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
16. (search strategy or search criteria or systematic search or study selection or data extraction).ab.
17. (search* adj4 literature).ab.
18. (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
19. ((pool* or combined) adj2 (data or trials or studies or results)).ab.
20. cochrane.jw.
21. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. 10 and 21

Appendix x – Search strategy used to identify potentially missed trials

1. dabigatran.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, ui]
2. pradaxa.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, ui]
3. rivaroxaban.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, ui]
4. xarelto.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, ui]
5. apixaban.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, ui]
6. Eliquis.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, ui]
7. Edoxaban.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, ui]
8. Lixiana.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, ui]
9. Savaysa.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, ui]
10. (betrixaban or PRT054021).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, an, eu, pm, ui]
11. (DU-176b or DU176b).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, an, eu, pm, ui]
12. (YM150 or YM-150 or LY517717 or LY-517717 or DU-176b or DU176*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, an, eu, pm, ui]
13. (GW813893 or “Tak 442” or TAK442 or PD0348292 or GSK-813893 or GSK813893).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, an, eu, pm, ui]
14. Factor Xa Inhibitors.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, an, eu, pm, ui]
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. Thrombosis.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, an, eu, pm, ui]
17. Thromboembolism.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, an, eu, pm, ui]
18. Venous Thromboembolism.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, an, eu, pm, ui]
19. Pulmonary Embolism.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, an, eu, pm, ui]
20. (PE or DVT or VTE).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, an, eu, pm, ui]
21. 16 or 17 or 18 or 19 or 20
22. randomized controlled trial.pt.
23. random allocation/
24. double-blind method/
25. single-blind method/
27. Randomi?ed controlled trial$.mp.
28. controlled clinical trial.pt.
29. ((singl$ or double$ or trebl$ or tripl$) adj25 (blind$ or mask$)).mp.
30. random$.mp.
31. placebo$.mp.
32. cross-over studies.sh.
33. latin square.tw.
34. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35. animals/ not humans/
36. 34 not 35
37. 15 and 21 and 36

38. limit 37 to yr="2015 -Current"