Evidence report for anticoagulation in nonvalvular atrial fibrillation

Prepared by EBSCO Information Services

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Content

Part 1 - Scoping

Methods

Using an established, structured template that delineates key elements for scoping (i.e., the population, interventions, and key outcomes to consider), we collaboratively agreed with UKSH on the scope of the present evidence report. Initial scoping was completed on September 14, 2018 and refined January 15, 2019 following feedback discussions with UKSH on structured templates for evidence review reports.

Results – Criteria Selection for Critical Appraisal

Population

Inclusion criteria

Patients with nonvalvular atrial fibrillation

Exclusion criteria

Valvular heart disease

Contraindications to anticoagulation (such as high risk of bleeding)

Intervention and Comparator

Vitamin K antagonist

The intervention is warfarin or other coumarin derivative such as phenprocoumon, acenocoumarol, or phenocoumarol, which are all vitamin K antagonists (VKAs) dosed based on the international normalized ratio (INR) and considered to have a class effect (i.e., there is no clinically-important difference between any of the coumarin derivatives). This will be collectively referred to as "warfarin" for ease of reference.

The comparator will be placebo or no treatment.

Dabigatran

The intervention is the direct thrombin inhibitor dabigatran.

The comparator will be a VKA.

Rivaroxaban

The intervention is the factor Xa inhibitor rivaroxaban.

The comparator will be a VKA.

Apixaban

The intervention is the factor Xa inhibitor apixaban.

The comparator will be a VKA.

Edoxaban

The intervention is the factor Xa inhibitor edoxaban.

The comparator will be a VKA.

Outcomes

FAQ 1: What does the treatment involve?

We will include a description of the treatment, including frequency of dosing, need for monitoring, and dietary considerations.

Descriptive responses are acceptable, and this does not involve systematic evidence searches, critical appraisal, or evidence synthesis.

FAQ 2: What is my risk of a thromboembolic/ischemic stroke?

The outcome of interest is the one-year risk of thromboembolic/ischemic stroke.

The risk with no treatment will be derived from a validated prediction model (CHA_2DS_2-VASc)[1-5] and use CHA_2DS_2-VASc scores of 2 and 4 as example values for use without individual patient calculation. The value of 2 is used because this is a common cut-point for guidelines to start recommending anticoagulation in patients with nonvalvular atrial fibrillation (some recommend starting as low as 1 non-sex risk factor).[1-3] The value of 4 is used because it was the most common score in a large, prospective validation study.[4]

The relative effect estimate with VKA will be determined from randomized trials compared to placebo or no treatment.

The relative effect estimate with all other anticoagulant options will be determined from randomized trials compared to VKA.

FAQ 3: Will I live longer or avoid dying from a specific cause because of treatment?

The outcome of interest is all-cause mortality, and if reported, cause-specific mortality. The absolute and relative effect estimates with VKA will be determined from randomized trials compared to placebo or no treatment.

The absolute and relative effect estimates with all other anticoagulant options will be determined from randomized trials compared to VKA.

FAQ 4: What is my risk of major bleeding?

The outcome of interest is one-year risk of a major hemorrhagic event.

For warfarin, the risk will be derived from a validated risk prediction model (HAS-BLED)[2-4] and use a HAS-BLED score of 2 as an example value for use without individual patient calculation. The value of 2 is used because it was the most common value in a large, prospective validation study.[4]

The relative effect estimate with all other anticoagulant options will be determined from randomized trials compared to VKA.

FAQ 5: Can the blood-thinning effect of the treatment be reversed?

We will provide information on whether there is an established mechanism to reverse the anticoagulant effect of the intervention in question. If a reversal agent is technically available but not widely available, this will also be noted.

Descriptive responses are acceptable, and this does not involve systematic evidence searches, critical appraisal, or evidence synthesis.

FAQ 6: What do I do if I need surgery or a procedure?

We will describe perioperative considerations for timing of medication adjustment.

Descriptive responses are acceptable, and this does not involve systematic evidence searches, critical appraisal, or evidence synthesis.

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[1] January CT, Wann LS, Alpert JS, et al.; ACC/AHA Task Force Members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation. 2014 Dec 2;130(23):2071-104.
[2] Kirchhof P, Benussi S, Kotecha D, et al.; ESC Scientific Document Group. 2016 ESC Guidelines for the Management of Atrial Fibrillation Developed in Collaboration With EACTS. Eur Heart J. 2016 Oct 7;37(38):2893-2962.
[3] Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. Chest. 2018 Nov;154(5):1121-1201.
[4] Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J. 2012 Jun;33(12):1500-10.
[5] van den Ham HA, Klungel OH, Singer DE, Leufkens HG, van Staa TP. Comparative Performance of ATRIA, CHADS2, and CHA2DS2-VASc Risk Scores Predicting Stroke in Patients With Atrial Fibrillation: Results From a National Primary Care Database. J Am Coll Cardiol. 2015 Oct 27;66(17):1851-9.

Part 2 - Search and Selection

Methods

First-round searching will consist of searching DynaMed Plus summaries pertinent to the topic. The search starts with DynaMed Plus because DynaMed Plus content is based on a thorough, systematic search and active literature surveillance system.

> Systematic literature surveillance (SLS) has been a cornerstone of creating DynaMed content since its inception. Currently, the SLS team works closely with members of McMaster University's Department of Health Research Methods, Evidence, and Impact to define and refine optimal search strategies, utilizing search terms for methodology and for clinical concepts (especially diagnosis and treatment) for each journal. These filters for PubMed searches are derived from PubMed Clinical Queries, McMaster University Hedges system, and DynaMed search filters and were found to capture >95% of relevant valid articles for use in DynaMed.[1]
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> [1]Alper BS, Iorio A. Optimising search filters for active literature surveillance: a concordance study. Global Evidence Summit. Cape Town, South Africa; September 2017.
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> The SLS team, in collaboration with McMaster University, continually evaluates and improves these filters to keep abreast of the ever-changing medical literature landscape. PubMed searches are performed daily. Each article is assessed by an external screener for clinical relevance, then reviewed by internal staff for both clinical relevance and validity. Any disagreements are settled by the Deputy Editor of the SLS team.
>
> In addition, the SLS team continually monitors the Journal source list against the list of journals catalogued in MEDLINE and existing DynaMed content to determine the set of journals that provide the highest yield for valid, clinically relevant content. As of November 2018, 507 Journals are systematically searched (see http://dynamed.com/home/content/content-sources). The journal selection threshold leads to routine adjustments to the number of journals selected.

Second-round searching will involve PubMed/MEDLINE® searches for intervention-specific systematic reviews that are more recent than those identified in first-round searching.

Third-round searching will involve original study tracing from systematic reviews, guidelines or other relevant sources. This may be done to identify additional evidence sources if the results from the first two rounds of searching are insufficient.

Fourth-round searching will involve searches for original evidence reports. Such searching will be limited to areas considered insufficiently addressed by earlier searches, such as focused concepts published after search dates in systematic reviews.

Additional selective searching, such as tracing citations from articles found or seeking related articles, may be done for additional concepts discovered.

FAQ Summary

Results

First-round searching – DynaMed Plus

DynaMed Plus subsection	Number of article citations	Number of studies included	Relevant for FAQ(s)
Thromboembolic prophylaxis in atrial fibrillation topic, Vitamin K Antagonists (VKAs) section, Efficacy (vs. no anticoagulant) subsection (January 18, 2019)	9	1 (Aguilar 2005)	FAQ1, FAQ2, FAQ3, FAQ4
Thromboembolic prophylaxis in atrial fibrillation topic, Direct Oral Anticoagulants section, Drug class efficacy (vs. VKA therapy) subsection (January 18, 2019)	21	1 (Bruins 2018)	FAQ1, FAQ2, FAQ3, FAQ4
Thromboembolic prophylaxis in atrial fibrillation topic, Direct Oral Anticoagulants section, Direct thrombin inhibitors subsection (January 17, 2019)	25	2 (Connolly 2009 [with corrections to outcome rates in Connolly 2010 and 2014], Salazar 2014)	FAQ1, FAQ2, FAQ3, FAQ4
Thromboembolic prophylaxis in atrial fibrillation topic, Direct Oral Anticoagulants section, Factor Xa inhibitors subsection, Rivaroxaban subsection (January 18, 2019)	18	3 (Cohen 2016, European Medicines Agency 2016, Patel 2011)	FAQ2, FAQ3, FAQ4
Thromboembolic prophylaxis in atrial fibrillation topic, Direct Oral Anticoagulants section, Factor Xa inhibitors subsection, Apixaban subsection (January 18, 2019)	21	2 (Granger 2011, Seife 2015)	FAQ2, FAQ3, FAQ4
Thromboembolic prophylaxis in atrial fibrillation topic, Direct Oral Anticoagulants section, Factor Xa inhibitors subsection, Edoxaban subsection (January 18, 2019)	13	1 (Giugliano 2013)	FAQ1, FAQ2, FAQ3, FAQ4

Thromboembolic prophylaxis in atrial fibrillation topic, Guidelines and Resources section, Guidelines subsection, United Kingdom guidelines subsection (January 18, 2019)	6	1 (NICE 2014)	FAQ1, FAQ2, FAQ3, FAQ4
Periprocedural management of patients on long-term anticoagulation topic, References section, General references used subsection (January 18, 2019)	7	1 (Doherty 2017)	FAQ6
Overanticoagulation management topic, References section, General references used subsection (January 18, 2019)	8	1 (Tomaselli 2017)	FAQ5

Second-round searching – searches for intervention-specific systematic reviews

Database	Search string	Number of search results	Number of studies included	Relevant for FAQ(s)
PubMed January 18, 2019	(warfarin OR coumarins) OR ("DOAC" OR "direct oral anticoagulant" OR "NOAC" OR "non vitamin K oral anticoagulant" OR "non vitamin K anticoagulant" OR "non-vitamin-K oral anticoagulant" OR "non-vitamin-K anticoagulant" OR "non-vitamin K oral anticoagulant" OR "non-vitamin K anticoagulant" OR "novel oral anticoagulant" OR "new oral anticoagulant") OR (dabigatran OR rivaroxaban OR apixaban OR edoxaban) AND ((reverse OR reversal OR reversing) OR (surgery OR surgical OR surgeon OR operative OR operation OR operating OR procedural OR periprocedural)) AND (systematic[sb] OR review[title] OR Guideline[ptyp] OR decision pathway[title]) AND ("2017/01/01"[PDAT] : "3000/12/31"[PDAT])	106	3 (Doherty 2017*, Verma 2018, Tornkvist 2018)	FAQ5, FAQ6

* already captured in first-round searching

Third-round searching – original study tracing from systematic reviews

Source	Tracing	Number of search results	Number of studies included	Relevant for FAQ(s)
Salazar 2014	Tracing trials of dabigatran (review included direct thrombin inhibitors that are not of interest)	3	1 (Connolly 2009* [with corrections to outcome rates in Connolly 2010 and 2014])	FAQ1, FAQ2, FAQ3, FAQ4
Bruins 2018	Tracing trials of apixaban, edoxaban, and rivaroxaban (review included factor Xa inhibitors that are not of interest and pooled separate doses of edoxaban)	8	3 (Giugliano 2013*, Granger 2011*, Patel 2011*)	FAQ1, FAQ2, FAQ3, FAQ4
NICE 2014	Confirmation of current systematic review and meta-analysis for warfarin versus control in nonvalvular atrial fibrillation	N/A; NICE 2014 confirmed Aguilar 2005 is a current systematic review and meta-analysis for warfarin versus control in nonvalvular atrial fibrillation, and no new relevant trials have been published since		FAQ2, FAQ3, FAQ4

* already captured in first-round searching

Fourth-round searching – searches for original evidence reports

Database	Search string	Number of search results	Number of studies included	Relevant for FAQ(s)
PubMed January 17, 2019	dabigatran AND (warfarin OR coumarins) AND atrial fibrillation AND Randomized Controlled Trial[ptyp] AND ("2013/04/01"[PDAT] : "3000/12/31"[PDAT])	48	0	FAQ2, FAQ3, FAQ4
PubMed January 18, 2019	(rivaroxaban OR apixaban OR edoxaban) AND (warfarin OR coumarins) AND (atrial fibrillation) AND Randomized Controlled Trial[ptyp] AND ("2016/08/01"[PDAT] : "3000/12/31"[PDAT])	45	0	FAQ2, FAQ3, FAQ4
PubMed January 18, 2019	(warfarin OR coumarins) AND (placebo OR control) AND (atrial fibrillation) NOT ("subgroup"[Title] OR "ROCKET-AF"[Title] OR "ARISTOTLE"[Title] OR "RE-LY"[Title] OR "ENGAGE AF-TIMI 48"[Title] OR "left atrial appendage"[Title] OR ablation OR cardioversion OR protocol[Title] OR design and rationale[Title] OR rationale and design[Title]) AND Randomized Controlled Trial[ptyp]	56	0	FAQ2, FAQ3

Part 3 - Critical Appraisal of Evidence Reports

Methods

For each study selected for critical appraisal, we assessed for criteria needed for Level 1 [likely reliable] evidence ratings in DynaMed's Levels of Evidence criteria in which evidence quality is labeled in 1 of 3 levels:

- **(level 1 [likely reliable] evidence)** for studies with clinical outcomes and minimal risk of bias;
- **(level 2 [mid-level] evidence)** for studies with clinical outcomes and significant methodological or statistical limitations; and
- **(level 3 [lacking direct] evidence)** for reports that do not include scientific analysis of clinical outcomes or for study types that do not include comparisons between groups.

The specific concepts we critically assessed are fully mapped to cover all the criteria used in GRADE. We summarized key concerns identified that reduce the certainty of evidence in categories used for GRADE methods (ie, risks of bias, indirectness, imprecision, inconsistency, and other considerations if relevant). In the study-level summaries inconsistency assessment was applied to consistency of within-study results – this applies to consistency across related outcomes for both original studies and for systematic reviews, and also applies to consistency across studies when applied to systematic reviews.

Characteristics and Results of Critically Appraised Studies/ Sources

AGUILAR 2005

Aguilar MI, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD001927. PubMed

Relevant to FAQ2, FAQ3

- **Study design:** systematic review
- **Population:** 2,313 adults (mean age 69 years) with nonvalvular atrial fibrillation and no history of stroke or transient ischemic attack (TIA) included in 5 randomized trials
- **Intervention:** warfarin (mean achieved INRs ranged between 2.0 and 2.6)
- **Comparison:** placebo in 4 trials; aspirin in 1 trial
- **Outcome:** ischemic stroke, myocardial infarction, systemic emboli, vascular death, intracranial hemorrhage, and major extracranial hemorrhage
- **Duration of follow-up:** mean 1.5 years
- **Certainty:**
  - **Risk of bias:** no serious concerns
  - **Precision:** wide confidence intervals for some outcomes
  - **Directness:** no serious concerns
  - **Consistency:** no serious concerns
  - **Other considerations:** This review has not been updated since 2005; however, the efficacy of warfarin has been established and no new randomized trials are being conducted on warfarin vs. placebo.
- **Results and certainty:**

Outcome	Sample Size (no. of trials)	Relative effect estimates*	Control group event rate	Certainty
all-cause mortality	**2,461 (5)**	**OR 0.69 (95% CI 0.5 to 0.94)** **RR 0.71 (95% CI 0.52 to 0.94)**	**99/1236 (8.01%)**	**High**
all ischemic stroke or intracranial hemorrhage	2,313 (5)	OR 0.39 (95% CI 0.26 to 0.59) RR 0.41 (95% CI 0.27 to 0.61)	71/1159 (6.13%)	High
all ischemic stroke (fatal and non-fatal)	**2,313 (5)**	**OR 0.34 (95% CI 0.23 to 0.52)** **RR 0.35 (95% CI 0.24 to 0.54)**	**69/1159 (5.95%)**	**High**
all disabling or fatal ischemic stroke or intracranial	2,313 (5)	OR 0.47 (95% CI 0.28 to 0.8) RR 0.48 (95% CI 0.29 to 0.81)	39/1159 (3.36%)	High

hemorrhage				
myocardial infarction	1,318 (3)	OR 0.87 (95% CI 0.32 to 2.42) RR 0.87 (95% CI 0.32 to 2.38)	8/660 (1.21%)	Low (downgraded due to serious imprecision)
systemic emboli	2,313 (5)	OR 0.45 (95% CI 0.13 to 1.57) RR 0.45 (95% CI 0.13 to 1.56)	7/1159 (0.60%)	Low (downgraded due to serious imprecision)
intracranial hemorrhage[†]	2,313 (5)	OR 2.38 (95% CI 0.54 to 10.5) RR 2.37 (95% CI 0.54 to 10.33)	2/1159 (0.17%)	Low (downgraded due to serious imprecision)
major extracranial bleeds[‡]	2,313 (5)	OR 1.07 (95% CI 0.53 to 2.12) RR 1.07 (95 CI 0.53 to 2.09)	16/1159 (1.38%)	Low (downgraded due to serious imprecision)
vascular death	**2,313 (5)**	**OR 0.84 (95% CI 0.56 to 1.27)** **RR 0.85 (95% CI 0.57 to 1.26)**	**51/1159 (4.40%)**	**Moderate (downgraded due to imprecision)**

[*] Aguilar 2005 reported OR data. We have converted these into RR data in the standard fashion using the OR data and the event rate in the control group.
[†] This outcome included intraparenchymal hemorrhage, subdural and epidural hematomas, and subarachnoid hemorrhage
[‡] Criteria for this outcome varied among included studies

BRUINS 2018

Bruins Slot KM, Berge E. Factor Xa inhibitors versus vitamin K antagonists for preventing cerebral or systemic embolism in patients with atrial fibrillation. Cochrane Database Syst Rev. 2018 Mar 6;3:CD008980. PubMed

Relevant to FAQ2, FAQ3, FAQ4

- **Study design:** systematic review
- **Population:** 13 trials totaling 67,688 participants with non-valvular atrial fibrillation and one or more risk factors for stroke (average age between 65 and 74 years; approximately 33% women)
- **Intervention:** factor Xa inhibitor (apixaban, betrixaban, darexaban, edoxaban, idraparinux, idrabiotaparinux, or rivaroxaban)
- **Comparison:** vitamin K antagonists
- **Outcome:** composite endpoint of all strokes (both ischemic and hemorrhagic) and non-central nervous system (non-CNS) systemic embolic events, all strokes (ischemic and hemorrhagic), ischemic strokes, all disabling or fatal strokes (ischemic or hemorrhagic), non-CNS systemic embolic events, major bleeding, intracranial hemorrhages (including intraparenchymal hemorrhage, subdural or epidural hematoma, and subarachnoid hemorrhage), non-major clinically-relevant bleeding, myocardial infarction, vascular death, all-cause death, and non-bleeding adverse events

- **Duration of follow-up:** median duration of follow-up ranged from 12 weeks to 2.8 years across all included trials; ARISTOTLE 2011 (Granger 2011) and ROCKET AF 2011 (Patel 2011) had median follow-up durations of 1.8 and 1.9 years, respectively
- **Considerations about this study:**
    - This review considered factor Xa inhibitors not relevant to this evidence review (betrixaban, darexaban, idraparinux, and idrabiotaparinux)
    - Of the 8 included trials that considered factor Xa inhibitors of interest (apixaban, edoxaban, and rivaroxaban), only 3 trials are relevant/appropriate to consider for the questions/outcomes of interest (one-year risk of thromboembolic/ischemic stroke, cause-specific or all-cause mortality, and one-year risk of major bleeding). Brief reasons include the following:
        - edoxaban (4 trials, 1 judged appropriate/relevant to consider):
            - 3 trials (Edoxaban Japan 2012, Edoxaban Asia 2011, and Edoxaban US/Europe 2010) only ran for 12 weeks/3 months, which carries a considerable risk of type II error for the questions/outcomes of interest. Additionally:
                - Edoxaban Japan 2012 was a phase II study with primary intent to assess safety, was limited to patients in Japan, and included a nonstandard dose of edoxaban (doses included 30 mg, 45 mg, or 60 mg once daily) and nonstandard dosing of warfarin (INR 2 to 3 for participants aged <70 years and 1.6 to 2.6 for participants aged ≥70 years, with mean age in warfarin group of 69 years); Edoxaban Asia 2011 was a phase II study primarily designed to assess the safety of edoxaban in Asian patients (and was thus limited to patients in four Asian countries); and Edoxaban US/Europe 2010 was also a phase II study with primary intent to assess safety, and included nonstandard doses of edoxaban (doses were 30 mg or 60 mg once or twice daily)
            - The authors of the systematic review also pooled the doses of edoxaban, which we consider inappropriate (corroborating evidence for this is in Giugliano 2013, as well as regulatory review documents publicly available but not reviewed here)
            - Only ENGAGE AF-TIMI 48 2013 was judged at low risk of bias for all domains by Bruins 2018. We agree it is more robust, and we add that ENGAGE AF-TIMI 48 was also more representative and much larger with capture of many more events than any of the other 3 trials noted above. It would thus dominate any meta-analysis including all 4 trials. This is evident in Bruin 2018's meta-analytic estimates, but we still consider these meta-analytic estimates less appropriate than considering the data from ENGAGE AF-TIMI 48.
            - Due to the above (including the inappropriate pooling of doses), we have summarized ENGAGE AF-TIMI 48 2013 separately (Giugliano 2013)
        - apixaban (2 trials, 1 judged appropriate/relevant to consider):
            - ARISTOTLE-J 2011 was a 12-week, phase II trial limited to Japanese patients with primary intent to assess safety. The 12-week duration is at considerable risk of type II error due to the questions/outcomes of interest, and it randomly assigned patients to warfarin, a standard dose of apixaban (5 mg twice daily), or a dose of apixaban that is only

recommended in specific circumstances based on the patient's age, weight, and/or renal function (2.5 mg twice daily).
        - ARISTOTLE 2011 (Granger 2011) was a much larger, more robust, longer, and more representative trial. Given its size and number of events recorded, it would thus dominate any meta-analysis including both trials. This is evident in Bruin 2018's meta-analytic estimates, but we still consider these meta-analytic estimates less appropriate than considering only the data from ARISTOTLE 2011 (Granger 2011) captured by Bruins 2018.
        - Due to the above, we only use the data from ARISTOTLE 2011 (Granger 2011) that are captured by Bruins 2018.
    - rivaroxaban (2 trials, 1 judged appropriate/relevant to consider):
        - J-ROCKET AF 2012 was limited to Japanese patients and utilized nonstandard doses of both rivaroxaban and warfarin: rivaroxaban 15 mg daily (10 mg daily in patients with CrCl 30 to 49 mL/min at baseline) or warfarin (dose-adjusted to INR of 2.0 to 3.0 in patients aged <70 years or 1.6 to 2.6 in patients aged ≥70 years, and mean age was 71 overall and within each group). Follow-up duration is unclear, but the survival curves show >50% still in the study at 1 year.
        - ROCKET AF 2011 (Patel 2011) was a much larger, more robust, and more representative trial. Given its size and number of events recorded, it would thus dominate any meta-analysis including both trials. This is evident in Bruin 2018's meta-analytic estimates, but we still consider these meta-analytic estimates less appropriate than considering only the data from ROCKET AF 2011 (Patel 2011) captured by Bruins 2018.
        - Due to the above, we only use the data from ROCKET AF 2011 (Patel 2011) that are captured by Bruins 2018.

- **Certainty:**
    - **Risk of bias:** Both ARISTOTLE 2011 (Granger 2011) and ROCKET AF 2011 (Patel 2011) are at possible risk of bias due to early discontinuation of the study drug: 25.3% in apixaban group vs. 27.5% in warfarin group in ARISTOTLE 2011 (Granger 2011), and 23.7% in rivaroxaban group vs. 22.2% in warfarin group in ROCKET AF 2011 (Patel 2011).
    - **Precision:** confidence intervals for certain outcomes include the possibility of both clinically-relevant benefit and clinically-relevant harm compared to warfarin; others include the possibility of clinically-relevant benefit or no benefit compared to warfarin
    - **Directness:** no serious concerns
    - **Consistency:** no serious concerns
    - **Other considerations:**
        - There were post-marketing concerns raised about the point-of-care monitoring of warfarin in ROCKET AF 2011 (Patel 2011), and although this has led some to call for independent reanalysis of the available data (Cohen 2016), the European Medicines Agency concluded that any incorrect INR measurements provided by the recalled devices would have marginal effects on the study outcomes, and therefore should not impact the safety or benefit-risk balance of rivaroxaban (EMA 2016).
        - There were concerns raised over completeness of follow-up and violations of good clinical practice in ARISTOTLE 2011 (Granger 2011), with one site in China having severe enough infractions that the Food and Drug Administration issued

an official action indicated (OAI) sanction, which is the harshest classification (Seife 2015).

- **Results:**

Outcome	apixaban vs. warfarin (n = 18,201)	rivaroxaban vs. warfarin (n = 14,264)
	(OR [95% CI]; events in warfarin group/total number in warfarin group)	**(OR [95% CI]; events in warfarin group/total number in warfarin group)**
	(RR [95% CI])	**(RR [95% CI])**
any stroke (ischemic or hemorrhagic) or non-CNS systemic embolic event	0.79 (0.66 to 0.95); 265/9081	0.88 (0.74 to 1.03); 306/7090
	0.80 (0.67 to 0.95)	0.88 (0.75 to 1.03)
all strokes (ischemic or hemorrhagic)	0.79 (0.65 to 0.95); 250/9081	0.83 (0.68 to 1.01); 221/7082
	0.79 (0.66 to 0.95)	0.84 (0.69 to 1.01)
ischemic stroke	**0.92 (0.74 to 1.14); 175/9081**	**0.93 (0.74 to 1.16); 161/7082**
	0.92 (0.75 to 1.14)	**0.93 (0.74 to 1.16)**
	Low certainty (high discontinuation rates and imprecision)	**Low certainty (high discontinuation rates and imprecision)**
disabling or fatal stroke	not reported	0.72 (0.55 to 0.95); 124/7082
		0.73 (0.56 to 0.95)
non-CNS systemic embolic events	0.88 (0.44 to 1.76); 17/9081	0.23 (0.09 to 0.60); 22/7082
	0.88 (0.44 to 1.76)	0.23 (0.09 to 0.60)
major bleeding	**0.69 (0.60 to 0.80); 462/9052**	**1.03 (0.89 to 1.19); 386/7125**
	0.70 (0.61 to 0.81)	**1.03 (0.89 to 1.18)**
	Moderate certainty (high discontinuation rates)	**Low certainty (high discontinuation rates and imprecision)**
intracranial hemorrhages	0.42 (0.30 to 0.58); 122/9052	0.65 (0.46 to 0.92); 84/7125
	0.42 (0.31 to 0.59)	0.66 (0.47 to 0.92)
non-major clinically	0.68 (0.58 to 0.79); 415/9052	1.04 (0.95 to 1.13); 1151/7125

relevant bleeding	0.69 (0.59 to 0.80)	1.03 (0.96 to 1.11)
myocardial infarction	0.88 (0.66 to 1.17); 102/9081	0.80 (0.62 to 1.04); 126/7082
	0.88 (0.66 to 1.16)	0.80 (0.62 to 1.04)
vascular death	**not reported**	**0.88 (0.71 to 1.09); 193/7082**
		0.88 (0.72 to 1.08)
		Low certainty* (high discontinuation rate and imprecision)
all-cause death	**0.89 (0.79 to 1.00); 669/9081**	**0.83 (0.69 to 1.00); 250/7082**
	0.90 (0.81 to 1.00)	**0.83 (0.70 to 1.00)**
	Low certainty* (high discontinuation rates and imprecision)	**Low certainty* (high discontinuation rates and imprecision)**

Data come from Bruin 2018's extracted data for ARISTOTLE 2011 (Granger 2011, n = 18,201; apixaban vs. warfarin) or ROCKET AF 2011 (Patel 2011, n = 14,264; rivaroxaban vs. warfarin) for reasons stated above. Items that are bolded were also assessed for certainty given their centrality to the defined questions/outcomes of interest.
* The threshold used to define certainty for these outcomes has an impact the certainty rating. For the outcomes marked with an *, the threshold used was the same as that used for all other outcomes, namely: "Is the medication *better than* warfarin?". Therefore, these outcomes were downgraded for imprecision, as the CI includes the possibility that there was either no benefit or no clinically-meaningful benefit compared to warfarin, or in one case (rivaroxaban vs. warfarin for the outcome of vascular death) the possibility of a worsening compared to warfarin that is of an uncertain clinical relevance (estimated rates appear later). If one instead used a threshold of "Is the medication *no worse than* warfarin?" all outcomes with an * may very well *not* be downgraded for imprecision (depending on what someone considers an acceptable threshold for noninferiority), which would then mean these outcomes would have Moderate certainty. Some imprecision is noted for rivaroxaban for vascular death, but the vast majority of the CI would suggest rivaroxaban is at least no worse than warfarin and may in fact offer benefit compared to warfarin, with CI bounds that translate to the possibility of anything from an approximate 0.22% absolute worsening compared to warfarin to an approximate 0.76% absolute improvement compared to warfarin.

COHEN 2016

Cohen D. Rivaroxaban: can we trust the evidence? BMJ. 2016 Feb 3;352:i575. PubMed
Relevant to FAQ2, FAQ3, FAQ4

> This was not critically appraised in full, because this was not an original study report or systematic review, but it did provide contextual information for critical appraisal of Bruins 2018. Specifically, there were post-marketing concerns raised about the point-of-care monitoring of warfarin in ROCKET AF, and although this has led some to call for independent reanalysis of the available data (Cohen 2016), the European Medicines Agency concluded that any incorrect INR measurements provided by the recalled devices would have marginal effects on the study

outcomes, and therefore should not impact the safety or benefit-risk balance of rivaroxaban (EMA 2016).

CONNOLLY 2009

Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;361(12):1139-51. PubMed Erratum in: N Engl J Med. 2010 Nov 4;363(19):1877. PubMed Erratum in: N Engl J Med. 2014 Oct 9;371(15):1464-5. PubMed (Both errata reported updated or additional event rate data, and corrected data have been incorporated into the summary below.) PubMed.

Relevant to FAQ2, FAQ3, FAQ4

- **Study design:** randomized trial
- **Population:** 18,113 patients (mean age 71 years, 64% men) with atrial fibrillation and ≥ 1 additional stroke risk factor(s) were randomized to 1 of 3 regimens
    - ≥ 1 of following stroke risk factors required to be eligible
        - previous stroke or transient ischemic attack (TIA)
        - left ventricular ejection fraction of less than 40%
        - New York Heart Association (NYHA) class II or higher heart-failure symptoms within 6 months before screening
        - age ≥ 75 years or aged 65-74 years with diabetes, hypertension, or coronary artery disease (CAD)
    - aspirin < 100 mg/day or other antiplatelet agents allowed
- **Intervention:** dabigatran 110 mg orally twice daily (n = 6,015) OR dabigatran 150 mg orally twice daily (n = 6,076) (patients were blinded to dabigatran dose)
- **Comparison:** warfarin adjusted dose for target INR 2-3 (not blinded) (n = 6,022)
- **Outcome:** all-cause stroke (ischemic or hemorrhagic) or systemic embolism, all-cause stroke, ischemic (or unspecified) stroke, hemorrhagic stroke, all-cause mortality, vascular mortality, major bleeding, gastrointestinal bleeding, life-threatening bleeding, non-life-threatening major bleeding, intracranial bleeding, extracranial bleeding, myocardial infarction, and adverse events (with only dyspepsia showing a clear difference between the dabigatran and warfarin groups)
- **Duration of follow-up:** median 2 years (99.9% completed follow-up)
- **Certainty:**
    - **Risk of bias:** warfarin administered in open-label fashion (blinded endpoint adjudication, but those in warfarin group may still have been treated differently during the trial due to knowledge of receiving warfarin vs. dabigatran)
    - **Precision:** wide confidence intervals for some outcomes (e.g., ischemic stroke for 110 mg)
    - **Directness:** no serious concerns
    - **Consistency:** no serious concerns
    - **Other considerations:** rates of discontinuation for 110 mg of dabigatran, 150 mg of dabigatran, and warfarin were 14.5%, 15.5%, and 10.2%, respectively
- **Results:**

Outcome	**dabigatran 150 mg (n = 6,076)**	**dabigatran 110 mg (n = 6,015)**	**warfarin (n = 6,022)**
	(absolute event rate per	**(absolute event rate per**	**(absolute event rate per year)**

	year [RR vs. warfarin])	**year [RR vs. warfarin])**	
all-cause stroke	1.01% (RR 0.64, 95% CI 0.51 to 0.81)	1.44% (RR 0.92, 95% CI 0.74 to 1.13)	1.57%
ischemic or unspecified stroke	**0.93%; (RR 0.76, 95% CI 0.59 to 0.97)**	**1.34% (RR 1.10, 95% CI 0.88 to 1.37)**	**1.22%**
	Certainty: Moderate (lack of blinding in warfarin group)	**Certainty: Low (lack of blinding in warfarin group and imprecision)**	
hemorrhagic stroke	0.1% (RR 0.26, 95% CI 0.14 to 0.49)	0.12% (RR 0.31, 95%CI 0.17 to 0.56)	0.38%
stroke or systemic embolism	1.12% (RR 0.65, 95% CI 0.52 to 0.81)	1.54% (RR 0.89, 95% CI 0.73 to 1.09)	1.72%
all-cause mortality	**3.64% (RR 0.88, 95% CI, 0.77 to 1.00)**	**3.75% (RR 0.91, 95% CI 0.8 to 1.03)**	**4.13%**
	Certainty: Low (lack of blinding and imprecision)	**Certainty: Low (lack of blinding and imprecision)**	
vascular mortality	**2.28% (RR 0.85, 95% CI 0.72 to 0.99)**	**2.43% (RR 0.9, 95% CI 0.77 to 1.06)**	**2.69%**
	Certainty: Moderate (lack of blinding)	**Certainty: Low (lack of blinding and imprecision)**	
major bleeding	**3.40% (RR 0.94, 95% CI 0.82 to 1.08)**	**2.92% (RR 0.8, 95% CI 0.7 to 0.93)**	**3.61%**
	Certainty: Low (lack of blinding in warfarin group and imprecision)	**Certainty: Moderate (lack of blinding in warfarin group)**	
gastrointestinal bleeding	1.51% (RR 1.5, 95% CI 1.19 to 1.89)	1.12% (RR 1.10, 95% CI 0.86 to 1.41)	1.02%
life threatening bleeding	1.52% (RR 0.81, 95% CI 0.67 to 0.99)	1.27% (RR 0.67, 95% CI 0.55 to 0.83)	1.87%
non-life-threatening major bleeding	1.88% vs. (RR 1.07, 95% CI 0.89 to 1.29)	1.66% (RR 0.94, 95% CI 0.78 to 1.15)	1.76%
intracranial bleeding	0.3% (RR 0.4, 95% CI 0.27 to 0.6)	0.23% (RR 0.31, 95% CI 0.2 to 0.47)	0.74%

extracranial bleeding	2.84% (RR 1.07, 95% CI 0.92 to 1.25)	2.51% (RR 0.94, 95% CI 0.8 to 1.1)	2.67%
myocardial infarction (counting both clinical and silent myocardial infarction)	0.81% (RR 1.27, 95% CI 0.94 to 1.71)	0.82% (RR 1.29, 95% CI 0.96 to 1.75)	0.64%
dyspepsia	11.3% (RR not reported, p < 0.001)	11.8% (RR not reported, p < 0.001)	5.8%

Items that are bolded were also assessed for certainty given their centrality to the defined questions/outcomes of interest.

DOHERTY 2017

Doherty JU, Gluckman TJ, Hucker WJ, Januzzi JL Jr, Ortel TL, Saxonhouse SJ, Spinler SA. 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation: A Report of the American College of Cardiology Clinical Expert Consensus Document Task Force. J Am Coll Cardiol. 2017 Feb 21;69(7):871-898. PubMed
Relevant to FAQ6

- **Study design:** expert consensus decision pathway
- **Population:** patients with nonvalvular atrial fibrillation on anticoagulation
- **Results:** This expert consensus decision pathway is a dedicated resource for periprocedural management of patients with nonvalvular atrial fibrillation who are on either a vitamin K antagonist (VKA; warfarin being the prototypical agent, but also including other coumarin derivatives or congeners) or direct oral anticoagulant (DOAC; apixaban, edoxaban, dabigatran, or rivaroxaban). The pathway involves 5 key questions: (1) whether to interrupt oral anticoagulation, (2) when to interrupt oral anticoagulation, (3) whether to bridge, (4) how to bridge, and (5) how to restart anticoagulation. Below, we address 4 of these 5 key questions for DOACs and VKAs; we have omitted the specifics of how to bridge, as that is beyond the scope of this evidence review. Doherty 2017 also provides an online appendix with common procedures and associated bleeding risk (which was reproduced, with permission, by Verma 2018).

DOACs

- Whether to interrupt

Whether to interrupt DOAC therapy

Patient has ≥1 increased-bleeding-risk feature*	Patient has no increased-bleeding-risk features* Assess the bleeding risk specific to the procedure	
	No clinically-important procedure-specific bleeding risk	Any other degree of procedure-specific bleeding risk (i.e., low, intermediate, high, or uncertain risk)
Interrupt DOAC therapy. Proceed to “When to interrupt”.	Perform the procedure without interrupting the DOAC, but time it at a	Interrupt DOAC therapy. Proceed to “When to interrupt”.

DOAC interval trough.

* Doherty 2017 suggests any of the following constitutes an increased risk: major bleed or intracranial hemorrhage within the past 3 months, platelet abnormality (quantitative or qualitative, including concomitant aspirin use), bleeding during previous bridging. We note that clinical judgment may also include other factors.

- When to interrupt
  - This consideration centers on 4 variables:
    - whether the patient is at increased bleeding risk (see "Whether to interrupt")
    - whether the DOAC is a direct thrombin inhibitor (dabigatran) or factor Xa inhibitor (apixaban, edoxaban, or rivaroxaban)
    - the patient's creatinine clearance
    - the bleeding risk specific to the procedure.
  - The table below captures suggested actions for patients ***without*** an increased bleeding risk. The withholding durations are based on the estimated half-life withholding times of 2 to 3 half-lives for low procedural bleeding risk and 4 to 5 half-lives for intermediate, high, or uncertain procedural bleeding risk. For patients ***with*** increased bleeding risk, there are insufficient data on best practices, and it is recommended that DOAC therapy be interrupted at least as long as determined by creatinine clearance as documented in the table below, and possibly longer, but clinicians must also use clinical judgment.

For patients *without* an increased bleeding risk: Estimated drug half-lives and recommended duration of discontinuation prior to procedure based on creatinine clearance and procedural bleeding risk

Drug	dabigatran					apixaban, edoxaban, or rivaroxaban		
CrCl, mL/min	≥80	50-79	30-49	15-29	<15*	≥30	15-29	<15*
Half-life, h	13	15	18	27	30	6-15	A: 17 E: 17 R: 9	A: 17 E: 10 to 17 R: 13
Procedural bleeding risk								
Low†	≥24 h	≥36 h	≥48 h	≥72 h	No data; consider measuring dTT and/or withholding ≥96 h	≥24 h	≥36 h	No data; consider measuring agent-specific anti Xa level and/or withholding ≥48 h
Intermediate, high, or uncertain†	≥48 h	≥72 h	≥96 h	≥120 h	No data; consider measuring dTT	≥48 h	No data; consider measuring agent-specific anti Xa level and/or withholding ≥72 h	

A, apixaban; CrCl, creatinine clearance; dTT, direct thrombin time; E, edoxaban; h, hours; mL/min, milliliters per minute; R, rivaroxaban

* Off-dialysis values reported for half-life; on-dialysis values not reported

† Durations shown are the recommended duration of discontinuation prior to the procedure based on the corresponding CrCl

For patients *<u>with</u>* increased bleeding risk: There are insufficient data on best practices. It is recommended that DOAC therapy be interrupted at least as long as determined by creatinine clearance as documented in the table above, and possibly longer. Use clinical judgment.

- Whether to bridge
    - Bridging is not indicated with DOAC therapy. This is due to their short half-lives (compared to VKAs). Figure 4 of Doherty 2017 specifically says bridging is not indicated, and this is consistent with clinical practice and the pharmacokinetic and -dynamic profiles of the DOACs. However, Doherty 2017 also reasonably allows for some ambiguity in the text of their guidance, and they also address possible delays in restarting the DOAC after the procedure, which may lead to consideration of a short-term parenteral anticoagulant being administered:

        Given the short-half lives of DOACs, bridging with a parenteral agent is rarely, if ever, needed prior to procedures. Reinitiation of these agents after the procedure, however, may need to be delayed owing to the risk of postprocedural bleeding. Reinitiation might also be delayed depending upon: 1) the need for additional procedures; and/or 2) the patient's ability to tolerate oral medications. In these latter 2 circumstances, a short-acting parenteral anticoagulant (e.g., unfractionated heparin [UFH]) may be needed either between procedures or post-procedure, when thrombotic risk remains high. Depending on the indication (e.g., venous thromboembolism prophylaxis), a prophylactic dose of UFH or LMWH may be sufficient. These are very specific scenarios that are uncommon in routine clinical practice.

- How to restart anticoagulation
    - Cardiac valve surgery is not considered here, because this would be an indication for VKA therapy; thus, restarting anticoagulation here would fall under the VKA pathway
    - Otherwise, the recommended actions are captured in the table below.

Restarting DOAC therapy after a procedure in a patient with complete hemostasis, no bleeding complications, no high-bleed-risk features, and no potential for a bleed at a catastrophic location (e.g., intracranial, intraspinal)*

Patient ***<u>cannot</u>*** tolerate oral medication		Patient ***<u>can</u>*** tolerate oral medication	
High postprocedural bleeding risk	***Low*** postprocedural bleeding risk	***High*** postprocedural bleeding risk	***Low*** postprocedural bleeding risk
Consider parenteral anticoagulation until oral medications are possible. Start parenteral agent within 48-72 hours following the procedure.† When tolerating oral medications, convert from parenteral agent to DOAC.	Consider parenteral anticoagulation until oral medications are possible. Start parenteral agent within 24 hours following the procedure.† When tolerating oral medications, convert from parenteral agent to DOAC.	Reasonable to reinitiate DOAC 48-72 hours after the procedure.†‡	Reasonable to reinitiate DOAC 24 hours after the procedure.† Consider using a reduced dose on the evening after the procedure.‡

* If any of these are present, then use clinical judgment in cooperation with the managing team and the proceduralist.
† At a dose based on postprocedural renal function
‡ In cooperation with the managing team and proceduralist

VKAs

- Whether to interrupt
    - First, assess whether the patient has an increased bleeding risk. Doherty 2017 suggests any 1 of the following constitutes an increased risk (though we note clinical judgment may include other factors): major bleed or intracranial hemorrhage within the past 3 months, platelet abnormality (quantitative or qualitative, including concomitant aspirin use), INR above therapeutic range, or bleeding during previous bridging or similar procedure
        - if yes, assess procedural bleed risk
            - if procedural bleed risk is either not clinically important or low
                - insufficient data on best practices; likely interrupt but consult with proceduralist
                - using clinical judgment, is there persistent concern for bleeding?
                - if yes, interrupt VKA therapy
                - if no, do not interrupt VKA therapy
            - if procedural bleed risk is intermediate, high, or uncertain, interrupt VKAs
        - if no, assess procedural bleed risk
            - if ether not clinically important or low, do not interrupt VKA therapy
            - if intermediate or high, interrupt VKA therapy
            - if uncertain
                - insufficient data on best practices; likely interrupt but consult with proceduralist
                - using clinical judgment, is there persistent concern for bleeding?
                - if yes, interrupt VKA therapy
                - if no, do not interrupt VKA therapy

- When to interrupt is determined by INR measurement 5-7 days prior to procedure
    - if INR at goal level (i.e., 2.0 to 2.5 or 2.0 to 3.0) or supratherapeutic
        - discontinue 5 days (at goal) or ≥5 days (supratherapeutic) prior to procedure depending on
            - current INR
            - time to procedure
            - desired INR for procedure
        - recheck INR 24 hours prior to procedure
    - if INR is subtherapeutic
        - discontinue 3-4 days prior to procedure
        - recheck INR 24 hours prior to procedure if normal INR is desired

- Whether to bridge

- Whether to bridge ultimately amounts to balancing increased risk of a thromboembolic event from being off anticoagulation with the increased risk of a major bleeding event in the periprocedural period. Part of this assessment for the patient with nonvalvular atrial fibrillation will include his/her predicted thromboembolic risk as assessed via CHA_2DS_2-VASc score, but other factors may be considered as well (e.g., the thromboembolic risk from the surgery/procedure itself).
- assess patient thrombotic risk definitions (as defined by Doherty 2017)
  - "low" if CHA_2DS_2-VASc score of 1-4 (annualized stroke risk <5%) and no prior thromboembolic event
  - "moderate" if CHA_2DS_2-VASc score of 5-6 (annualized stroke risk 5%-10%) or prior thromboembolic event >3 months previously
  - "high" if CHA_2DS_2-VASc score of 7 or more (annualized stroke risk >10%) or prior thromboembolic event $\leq$3 months previously
- assess patient bleed risk, considered increased if $\geq$1 of following
  - major bleed or intracranial hemorrhage <3 months
  - quantitative or qualitative platelet abnormality including aspirin use
  - INR above therapeutic range
  - prior bleed from previous bridging
- outside of instances where there is either a clear indication or contraindication to bridging, the choice to bridge is based on assessment of patient thrombotic risk and patient bleed risk to determine whether the balance of benefits and harms favors bridging or not bridging; Doherty 2017 provides suggestions for situations where the decision is "likely bridge" or "likely do not bridge", but then ends with "use clinical judgement"

- When and how to restart anticoagulation
  - assess whether complete hemostasis was achieved, with no bleeding complications, no high-risk features of patient, and no potentially catastrophic bleed location (e.g., intracranial, intraspinal)
    - if no, consider delaying restarting anticoagulation; use clinical judgment in cooperation with managing team and proceduralist
    - if yes, assess whether plan or indication to give parenteral agent following procedure
      - if no, start VKA within 24 hours in cooperation with managing team and proceduralist
      - if yes, assess postprocedural bleed risk
        - if high postprocedural bleed risk
          - start VKA within 24 hours
          - restart parenteral agent if applicable 48-72 hours after procedure
          - discontinue parenteral agent when INR reaches 2
        - if low postprocedural bleed risk
          - start VKA within 24 hours
          - restart parenteral agent if applicable $\leq$24 hours after procedure
          - discontinue parenteral agent when INR reaches 2

EMA 2016

European Medicines Agency. EMA concludes defective device in ROCKET study does not impact Xarelto's safety. Published date: May 2, 2016. Last updated: May 2, 2016. Available from https://www.ema.europa.eu/en/news/ema-concludes-defective-device-rocket-study-does-not-impact-xareltos-safety.

Relevant to FAQ2, FAQ3, FAQ4

> This was not critically appraised in full, because this was not an original study report or systematic review, but it did provide contextual information for critical appraisal of Bruins 2018. Specifically, there were post-marketing concerns raised about the point-of-care monitoring of warfarin in ROCKET AF, and although this has led some to call for independent reanalysis of the available data (Cohen 2016), the European Medicines Agency concluded that any incorrect INR measurements provided by the recalled devices would have marginal effects on the study outcomes, and therefore should not impact the safety or benefit-risk balance of rivaroxaban (EMA 2016).

GIUGLIANO 2013

Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013 Nov 28;369(22):2093-104. Epub 2013 Nov 19. PubMed

Relevant to FAQ2, FAQ3, FAQ4

- **Study design:** randomized trial
- **Population:** 21,105 patients > 21 years old with moderate-to-high risk atrial fibrillation (CHADs2 risk assessment score ≥ 2) randomized to 1 of 3 interventions once daily
- **Intervention:** edoxaban 60 mg (high dose) (n = 7,035) OR edoxaban 30 mg (low dose) (n = 7,034)
- **Comparison:** warfarin (dose-adjusted to achieve international normalized ratio 2-3) (n = 7,036)
- **Outcomes:** stroke or systemic embolism, ischemic stroke, major bleeding, major gastrointestinal bleeding, intracranial bleeding, clinically relevant nonmajor bleeding, and any overt bleeding
- **Duration of follow-up:** median 2.8 years
- **Additional comments about methods:**
  - edoxaban dose decreased by 50% in patients with estimated creatinine clearance 30-50 mL/minute body weight < 60 kg (132 lbs), or concomitant use of verapamil or quinidine
  - trial designed to test noninferiority of edoxaban, but superiority tests performed after noninferiority criteria were met
- **Certainty:**
  - **Risk of bias:** 33%-34.5% in each group discontinued study medication
  - **Precision:** wide confidence intervals for certain outcomes (e.g., ischemic stroke for edoxaban 60 mg)
  - **Directness:** no serious concern
  - **Consistency:** no serious concern
- **Results:**

Outcome	**edoxaban 60 mg (n = 7,035)**	**edoxaban 30 mg (n = 7,034)**	**warfarin (n = 7,036)** **(absolute event rate**

	(absolute event rate per year [RR vs. warfarin])	**(absolute event rate per year [RR vs. warfarin])**	**per year)**
stroke or systemic embolism	1.18% (RR 0.79, 95% CI 0.63 to 0.99)	1.61% (RR 1.07, 95% CI 0.87 to 1.31)	1.5%
ischemic stroke	**1.25% (RR 1, 95% CI 0.83 to 1.19)**	**1.77% (RR 1.41, 95% CI 1.19 to 1.67)**	**1.25%**
	Certainty: Low (high discontinuation rates and imprecision)	**Certainty: Moderate (high discontinuation rates)**	
fatal stroke	**0.42% (RR 0.92, 95% CI 0.68 to 1.25)**	**0.38% (RR 0.84, 95% CI 0.61 to 1.15)**	**0.45%**
	Certainty: Low (high discontinuation rates and imprecision)	**Certainty: Low (high discontinuation rates and imprecision)**	
major bleeding	**2.75% (RR 0.8, 95% CI 0.71 to 0.91)**	**1.61% (RR 0.47, 95% CI 0.41 to 0.55)**	**3.43%**
	Certainty: Moderate (high discontinuation rates)	**Certainty: Moderate (high discontinuation rates)**	
major gastrointestinal bleeding	1.51% (RR 1.23, 95% CI 1.02 to 1.50)	0.82% (RR 0.67, 95% CI 0.53 to 0.83)	1.23%
intracranial bleeding	0.39% (RR 0.47, 95% CI 0.34 to 0.63)	0.26% (RR 0.3, 95% CI 0.21 to 0.43)	0.85%
clinically relevant nonmajor bleeding	8.67% (RR 0.86, 95% CI 0.79 to 0.93)	6.6% (RR 0.66, 95% CI 0.6 to 0.71)	10.15%
overt bleeding	14.15% (RR 0.87, 95% CI 0.82 to 0.92)	10.68% (RR 0.66, 95% CI0.62 to 0.71)	16.4%
death from cardiovascular causes	**2.74% (RR 0.85, 95% CI 0.77 to 0.97)**	**2.71% (RR 0.85, 95% CI 0.76 to 0.96)**	**3.17%**
	Certainty: Moderate (high discontinuation rates)	**Certainty: Moderate (high discontinuation rates)**	

death from any cause	**3.99% (RR 0.92, 95% CI 0.83 to 1.01)**	**3.80% (RR 0.87, 95% CI 0.79 to 0.96)**	**4.35%**
	Certainty: Low (high discontinuation rates and imprecision)	**Certainty: Moderate (high discontinuation rates)**	

Items that are bolded were also assessed for certainty given their centrality to the defined questions/outcomes of interest.

GRANGER 2011

Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011 Sep 15;365(11):981-92. PubMed
Relevant to FAQ2, FAQ3, FAQ4

> This is the pivotal ARISTOTLE trial for apixaban vs. warfarin in nonvalvular atrial fibrillation. We do not provide a full study summary here, because this trial was captured/included by Bruins 2018. Please see that entry for details.

NICE 2014

National Institute for Health and Care Excellence. Atrial fibrillation: management. Clinical guideline [CG180] Published date: June 2014 Last updated: August 2014. Available from https://www.nice.org.uk/guidance/cg180.
Relevant to FAQ2, FA3, FAQ4

- **Study design:** systematic review and guideline
- **Brief considerations about this review:**

  This guideline was mainly used to ensure that Aguilar 2005 was a current systematic review and meta-analysis and that no new trials had been published since. This was confirmed by the NICE 2014 systematic review and guideline document. NICE 2014 also noted another Cochrane review published prior to Aguilar 2005 (Saxena 2004), which is also captured by DynaMed Plus, but we did not include it for detailed consideration here. Saxena 2004 was limited to secondary prevention data (i.e., patients who had previously had a stroke or transient ischemic attack) from 2 trials totaling 485 patients, and 91% of the patient data (439 patients) came from 1 trial (EAFT 1993), which we also note used an INR goal of 2.5 to 4.0 and had a substantial proportion of reported INR values and person-years in INR range at or above 3.0 (only 60% of patients on anticoagulants had 50% or more of their INR values below 3.0, and the typical INR goal in nonvalvular atrial fibrillation is 2.5, with a range from 2 to 3). Saxena 2004 also reported recurrent stroke for its stroke outcome (thereby precluding ascertainment of ischemic stroke separately from hemorrhagic stroke), and the original data in EAFT 1993 reported effects on ischemic stroke similar to that reported by Aguilar 2005 (16/225 in anticoagulant group vs. 39/214 in control; RR 0.39, 95% CI 0.22 to 0.68). On that note,

even if considering these data (NICE 2014 did this as part of their guideline efforts), this yielded either:

- results that were not materially different from Aguilar 2005 for the questions/outcomes of interest
    - thromboembolic/ischemic stroke (RR 0.33, 95% CI 0.21 to 0.53, control group risk 5.5%)
    - all-cause mortality (RR 0.78, 95% CI 0.62 to 0.98, control group risk 10%)
    - cause-specific mortality not reported

or

- results that were different but still did not materially impact the questions/outcomes of interest and would raise question about how the INR goal in EAFT 1993 may have impacted results
    - major bleeding (RR 1.56, 95% CI 0.88 to 2.75, control group risk 1.4%) when NICE 2014 included the data from both Aguilar 2005 and Saxena 2004 in a combined meta-analysis for the outcome of major bleeding, but major bleeding on warfarin is to be estimated via HAS-BLED as specified in Part 1 Scoping, so this change is irrelevant, and we again note the possible issues with the INR goal range for EAFT 1993 and how that could affect bleeding outcomes (even the EAFT authors seem to have noted this, contributing to their 1995 publication seeking to find the INR that best balanced reduction in ischemic events with increase in bleeding events).

PATEL 2011

Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011 Sep 8;365(10):883-91. PubMed

Relevant to FAQ2, FAQ3, FAQ4

This is the pivotal ROCKET AF trial for rivaroxaban vs. warfarin in nonvalvular atrial fibrillation. We do not provide a full study summary here, because this trial was captured/included by Bruins 2018. Please see that entry for details.

SALAZAR 2014

Salazar CA, del Aguila D, Cordova EG. Direct thrombin inhibitors versus vitamin K antagonists for preventing cerebral or systemic embolism in people with non-valvular atrial fibrillation. Cochrane Database Syst Rev. 2014 Mar 27;(3):CD009893. PubMed

Relevant to FAQ2, FAQ3, FAQ4

- **Study design:** systematic review
- **Population:** 8 trials totaling 27,557 participants with non-valvular atrial fibrillation and one or more risk factors for stroke (mean age in all studies was over 70 years; 39% women)
- **Intervention:** direct thrombin inhibitors (dabigatran, AZD0837, and ximelagatran)
- **Comparison:** vitamin K antagonists
- **Outcome:** composite outcome of vascular deaths and ischemic events, composite outcome of fatal or non-fatal major bleeding events, fatal or non-fatal adverse events other than ischemic or

hemorrhagic events that led to discontinuation of treatment, death from all causes during treatment

- **Duration of follow-up:** studies planned outcome assessment over 2.8 to 24 months for dabigatran, 3 to 4.7 months for AZD0837, and 3 to 20 months for ximelagatran. Follow-up periods after discontinuation of study medication ranged from 0 to 4 weeks
- **Brief considerations about this study:**

  Only 3 trials included in this systematic review pertained to dabigatran, and only 1 (Connolly 2009) is appropriate for consideration for this Evidence Review. The other 2 trials (NCT01136408 and Petro 2007) both only ran for 12 weeks (compared to Connolly 2009's median 2-year follow-up, with 99.9% complete follow-up). Trials running for 12 weeks are at considerable risk of type II error for the questions/outcomes of interest (one-year risk of thromboembolic/ischemic stroke, cause-specific or all-cause mortality, and one-year risk of major bleeding). Moreover, NCT01136408 was an open label, randomized exploratory dose-response study with a primary intent to assess safety, and Petro 2007 was a randomized, dose-guiding safety study that also included nonstandard doses of dabigatran and receipt of aspirin (dabigatran at doses of 50, 150 and 300 mg twice daily combined in a 3 x 3 factorial fashion with no aspirin, 81 mg aspirin, or 325 mg aspirin every day). Additionally, although Connolly 2009 also had methodologic considerations, it was more methodologically robust than NCT01136408 and Petro 2007. Considering all of this, a meta-analysis of the 3 trials together would be more likely to add noise than meaningful insight compared to considering Connolly 2009 alone. The other 2 trials also contribute minimally to estimates of efficacy and safety compared to Connolly 2009 (i.e., meta-analysis with all 3 trials would be dominated by Connolly 2009, which can be seen in Salazar 2014's meta-analytic estimates, but we still consider it more appropriate to use Connolly 2009's data directly rather than Salazar 2014's meta-analytic estimates).

SEIFE 2015

Seife C. Research misconduct identified by the US Food and Drug Administration: out of sight, out of mind, out of the peer-reviewed literature. JAMA Intern Med. 2015 Apr;175(4):567-77. PubMed
Relevant to FAQ2, FAQ3, FAQ4

This was not critically appraised in full, but it does provide contextual information for interpreting Bruins 2018. Specifically, Seife 2015 raised concerns raised over completeness of follow-up and violations of good clinical practice in ARISTOTLE 2011 (Granger 2011), with one site in China having severe enough infractions that the Food and Drug Administration issued an official action indicated (OAI) sanction, which is the harshest classification.

TOMASELLI 2017

Tomaselli GF, Mahaffey KW, Cuker A, et al. 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol. 2017 Dec 19;70(24):3042-3067. PubMed
Relevant to FAQ5

We do not provide a full summary here, as this reference was used as part of answering FAQ5, which amounted to a descriptive evidence review, and there was little value in summarizing Tomaselli 2017's contribution both here and in Part 4.

TORNKVIST 2018
Tornkvist M, Smith JG, Labaf A. Current evidence of oral anticoagulant reversal: A systematic review. Thromb Res. 2018 Feb;162:22-31. PubMed
Relevant to FAQ5

We do not provide a full summary here, as this reference was used as part of answering FAQ5, which amounted to a descriptive evidence review, and there was little value in summarizing Tornkvist 2018's contribution both here and in Part 4.

VERMA 2018
Verma A, Ha ACT, Rutka JT, Verma S. What Surgeons Should Know About Non-Vitamin K Oral Anticoagulants: A Review. JAMA Surg. 2018 Jun 1;153(6):577-585. PubMed
Relevant to FAQ5

We do not provide a full summary here, as this reference was used as part of answering FAQ5, which amounted to a descriptive evidence review, and there was little value in summarizing Verma 2018's contribution both here and in Part 4. Verma 2018 also provided considerations for the perioperative period (FAQ6), but Doherty 2017 addressed this in more detail and with specific regard to patients with nonvalvular atrial fibrillation, and we do provide a more detailed summary of Doherty 2017.

Part 4 - Evidence Review

Methods

For each FAQ, the key concepts (results and factors affecting certainty of the results) from the critically appraised studies that are most relevant to evidence synthesis will be summarized in Evidence Review Tables. Where evidence is very limited, or the FAQ is for descriptive summary, summary text will be provided.

Results

FAQ 1: What does the treatment involve?

Descriptive Evidence Details

The treatment details below do not address how these medications might be adjusted if a person is taking additional medication, as this is beyond the scope of this evidence report.

For all oral anticoagulant medications, avoiding excessive alcohol intake is generally recommended due to the potential for increased risk of bleeding (the liver is responsible for synthesis of clotting factors and involved in metabolism of medications).

Vitamin K antagonist

You will take a pill daily at the same time each day. You can take it with or without food. You will need regular blood tests to measure how well the medication is working, with the frequency depending on the consistency of the results from the blood test. The dose of your medication may vary from day to day (e.g., 5 mg on Monday, Wednesday, and Friday, and 2 mg on Tuesday, Thursday, Saturday, and Sunday), and adjustments to the dose you take may be necessary based on the results of your blood test. Because the medication works by interfering with vitamin K, you need to maintain a consistent intake of foods containing vitamin K.

(American Heart Association 2016; DynaMed Plus 2018, Warfarin [drug information])

Apixaban

You will take a pill twice a day at the same time each day (i.e., morning and evening). You can take it with or without food. You will not need routine blood tests to see how well the medication is working. However, you may need a dose adjustment based on your kidney function*. Your health care practitioner will check your kidney function before starting the medication and at times while on the medication to ensure you are on the right dose. Your kidney function will typically be measured at least once or twice a year, but it may have to be monitored more regularly (e.g., every 3 months) depending on other conditions you may have or medications you may take. The adjustment in dose that may be required for this medication is more straightforward and less prone to fluctuate than the dose adjustments that can be required for vitamin K antagonists. There are no dietary considerations for this medication.

*Dose reduction is not indicated based on kidney function alone, but rather, in patients with ≥2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or moderate reduction in kidney function (defined as serum creatinine ≥1.5 mg/dL [133 mcmol/L]).

(Conway 2017; DynaMed Plus 2018, Apixaban [drug information]; January 2014; Lane 2015)

Dabigatran

You will take a pill twice a day. You can take it with or without food, but some recommend taking it with food to decrease stomach upset. Dose reduction is recommended in patients with certain degrees of renal impairment. However, you may need a dose adjustment based on your kidney function. Your health care practitioner will check your kidney function before starting the medication and at times while on the medication to ensure you are on the right dose. Your kidney function will typically be measured at least once or twice a year, but it may have to be monitored more regularly (e.g., every 3 months) depending on other conditions you may have or medications you may take. The adjustment in dose that may be required for this medication is more straightforward and less prone to fluctuate than the dose adjustments that can be required for vitamin K antagonists. There are no dietary considerations for this medication.

(Conway 2017; DynaMed Plus 2018, Dabigatran [drug information]; January 2014; Lane 2015)

Edoxaban

You will take a pill once a day at same time each day, with or after food. Dose reduction is recommended in patients with certain degrees of renal impairment, and edoxaban is contraindicated in patients with CrCl >95 mL/min. You will not need routine blood tests to see how well the medication is working. However, you may need a dose adjustment based on your kidney function. Your health care practitioner will check your kidney function before starting the medication and at times while on the medication to ensure you are on the right dose. Your kidney function will typically be measured at least once or twice a year, but it may have to be monitored more regularly (e.g., every 3 months) depending on other conditions you may have or medications you may take. The adjustment in dose that may be required for this medication is more straightforward and less prone to fluctuate than the dose adjustments that can be required for vitamin K antagonists. There are no dietary considerations for this medication.

(Conway 2017; DynaMed Plus 2018, Edoxaban [drug information]; January 2014; Lane 2015)

Rivaroxaban

You will take a pill once a day at same time each day, with or after food. Dose reduction is recommended in patients with certain degrees of renal impairment. You will not need routine blood tests to see how well the medication is working. However, you may need a dose adjustment based on your kidney function. Your health care practitioner will check your kidney function before starting the medication and at times while on the medication to ensure you are on the right dose. Your kidney function will typically be measured at least once or twice a year, but it may have to be monitored more regularly (e.g., every 3 months) depending on other conditions you may have or medications you may take. The adjustment in dose that may be required for this medication is more straightforward and less prone to fluctuate than the dose adjustments that can be required for vitamin K antagonists. There are no dietary considerations for this medication.

(Conway 2017; DynaMed Plus 2018, Rivaroxaban [drug information]; January 2014; Lane 2015)

during this part of the procedure, such as a slight burning sensation or heaviness in your chest. If this occurs, you can inform the nurse, physician, or other caregiver in the room, and they can give you more medication if needed.

The procedure itself may generally last 4 to 6 hours, but each patient is different. After the procedure, you will stay in bed for several hours and will need to keep your legs still to help prevent bleeding at the catheter insertion area. You will stay in the hospital overnight, but can normally go home the next day. You may have general soreness, some chest discomfort, and/or fatigue in the first 48 hours or so after the procedure. Additionally, because it takes time for the scar tissue to form, it is common for people to have extra or irregular heartbeats in the first 8 to 10 weeks after the procedure. You can usually return to normal, general activities 48 hours after the procedure, but you will probably be given restrictions on the weight you are allowed to lift for at least the first week and will probably need to refrain from vigorous exercise for at least 3 weeks.

Your healthcare team will also tell you about medications you will need to take after the procedure. You should expect to take a blood thinning medication for about 2 to 3 months after the procedure, and you may have to take this for even longer depending on your specific risk factors for stroke. You may also need to take a medication to help prevent abnormal heart rhythms for about 1 to 3 months.

The long-term goal of PVI is to reduce or eliminate the medications used to treat atrial fibrillation. Ideally, the procedure allows the patient to eliminate medications that help manage or treat the abnormal electrical signals that cause atrial fibrillation. Many patients are also ultimately able to stop their blood thinner (if they take one), but again, this will be assessed on a case-by-case basis. However, atrial fibrillation comes back and requires additional treatment in some patients.

(Calkins 2012; Calkins 2017; Cleveland Clinic 2017; Dudley 2014; University Hospital Southampton NHS Foundation Trust 2015)

Medical therapy (FAQ1b)

Descriptive Overview

Your healthcare professional will discuss two areas with you where medication is used for atrial fibrillation. The first area has to do with the abnormal electrical signals of atrial fibrillation. The second area has to do with how atrial fibrillation increases your risk for blood clots, which can cause stroke or block the flow of blood to other areas of your body (such as your arms or legs).
For the first area, you will either take a “rhythm control” or “rate control” medication. “Rhythm control” medications try to keep atrial fibrillation from occurring. “Rate control” medications try to keep the heart rate controlled even if atrial fibrillation occurs. Either is an acceptable choice, so you and your healthcare professional will decide which is best for you based on things like your other health conditions, cost, side effects, and other factors. For the second area, you and your healthcare professional will determine your risk of blood clots due to your atrial fibrillation. The risk is different for each person. If your risk of blood clots is high, you and your healthcare professional will discuss going on a medication to thin your blood.
(DynaMed Plus 2018; January 2014; Kirchhof 2016)

FAQ 2: What is my risk of a thromboembolic/ischemic stroke?

The one-year risk of a thromboembolic/ischemic stroke with no treatment is estimated via the CHA_2DS_2-VASc risk prediction model, as specified in Part 1 Scoping. Specifically, the estimated one-year risks without treatment that are presented here come from Friberg 2012's large, prospective validation study, using a CHA_2DS_2-VASc score of 2 (a common threshold where guidelines begin recommending oral anticoagulation) and 4 (the most common score in Friberg 2012's large, prospective validation study) as example scores (as specified in Part 1 Scoping). These scores correspond to estimated one-year risks without treatment of 2.5% and 5.5%, respectively.

To estimate the one-year risk of a thromboembolic/ischemic stroke when taking warfarin, the above-noted one-year risks with no treatment are adjusted by the relative risk data for warfarin vs. control. For example, for the CHA_2DS_2-VASc score of 2, the one-year risk without treatment of 2.5% is multiplied by the relative risk for warfarin vs. control of 0.35 to yield 0.88% as a point estimate for the one-year risk while on warfarin; this process is repeated for the lower and upper bounds of the relative risk confidence interval for warfarin vs. control.

Evidence Review Table – Vitamin K Antagonists

One-year thromboembolic/ischemic stroke risk when taking warfarin

Medication (sample size; no. studies; reference)	**Certainty**	**Relative risk (vs. control)**	**With an estimated one-year risk without treatment of 2.5% (CHA_2DS_2-VASc of 2), the one-year risk while taking warfarin is estimated to be**	**With an estimated one-year risk without treatment of 5.5% (CHA_2DS_2-VASc of 4), the one-year risk while taking warfarin is estimated to be**
warfarin (2,313; 5; Aguilar 2005)	High	**RR 0.35 (95% CI 0.24 to 0.54)**	**0.88% (95% CI 0.60% to 1.35%)**	**1.93% (95% CI 1.32% to 2.97%)**

Statistically-significant effects are **bolded**.

To estimate the one-year risk of a thromboembolic/ischemic stroke while taking each of the respective direct oral anticoagulants (DOACs; apixaban, dabigatran, edoxaban, and rivaroxaban), the above-noted point estimates for one-year risk while on warfarin (i.e., 0.88% for CHA_2DS_2-VASc score of 2 and 1.93% for CHA_2DS_2-VASc score of 4) are adjusted by the relative risk data for each of the DOACs vs. warfarin. For example, for the CHA_2DS_2-VASc score of 2, the one-year risk of 0.88% while on warfarin is multiplied by the relative risk of 0.92 for apixaban vs. warfarin to yield 0.81% as a point estimate for the one-year risk while on apixaban; this process is repeated with the lower and upper bounds of the relative risk confidence interval for apixaban vs. warfarin.

Evidence Review Table – Apixaban, Dabigatran, Edoxaban, Rivaroxaban

One-year risk of a thromboembolic/ischemic stroke when taking apixaban, dabigatran, edoxaban, or rivaroxaban

Medication (sample size; no. studies; reference)*	**Certainty**	**Relative risk (vs. warfarin)**	**Based on the estimated one-year risk of 0.88% while on warfarin with a CHA_2DS_2-VASc of 2, the estimated one-year risk while taking the respective DOAC is estimated to be:**	**Based on the estimated one-year risk of 1.93% while on warfarin with a CHA_2DS_2-VASc of 4, the estimated one-year risk while taking the respective DOAC is estimated to be:**
apixaban (18,201; 1; Bruins 2018)	Low (high discontinuation rates and imprecision)	RR 0.92 (95% CI 0.75 to 1.14)	0.81% (95% CI 0.66% to 1%)	1.78% (95% CI 1.45% to 2.2%)
dabigatran 150 mg (18,113; 1; Connolly 2009)	Moderate (lack of blinding in warfarin group)	**RR 0.76 (95% CI 0.59 to 0.97)**	**0.67% (95% CI 0.52% to 0.85%)**	**1.47% (95% CI 1.14% to 1.87%)**
dabigatran 110 mg (18,113; 1; Connolly 2009)	Low (lack of blinding in warfarin group and imprecision)	RR 1.10 (95% CI 0.88 to 1.37)	0.97% (95% CI 0.77% to 1.21%)	2.12% (95% CI 1.7% to 2.64%)
edoxaban 60 mg (21,105; 1; Giugliano 2013)	Low (high discontinuation rates and imprecision)	RR 1.00 (95% CI 0.83 to 1.19)	0.88% (95% CI 0.73% to 1.05%)	1.93% (95% CI 1.6% to 2.3%)
edoxaban 30 mg (21,105; 1; Giugliano 2013)	Moderate (high discontinuation rates)	**RR 1.41 (95% CI 1.19 to 1.67)**	**1.24% (95% CI 1.05% to 1.47%)**	**2.72% (95% CI 2.3% to 3.22%)**
rivaroxaban (14,264; 1; Bruins 2018)	Low (high discontinuation rates and imprecision)	RR 0.93 (95% CI 0.74 to 1.16)	0.82% (95% CI 0.65% to 1.02%)	1.79% (95% CI 1.43% to 2.24%)

Statistically-significant effects are **bolded**. *Note this includes the signal for a statistically-significantly worse rate of one-year thromboembolic/ischemic stroke outcomes with edoxaban 30 mg.*

***** The number listed for sample size is the total number randomized. However, for dabigatran and edoxaban, the data come from 3-armed trials studying 2 different doses of the respective DOAC versus warfarin. The number in each group is as follows: dabigatran 150 mg (n = 6,076), dabigatran 110 mg (n = 6,015), warfarin (n = 6,022); edoxaban 60 mg (n = 7,035), edoxaban 30 mg (n = 7,034), warfarin (n = 7,036).

FAQ 3: Will I live longer or avoid dying from a specific cause because of treatment?

Evidence Review Table – Vitamin K Antagonists, Apixaban, Dabigatran, Edoxaban, and Rivaroxaban

Mortality outcomes for warfarin versus control and apixaban, dabigatran, edoxaban, and rivaroxaban versus warfarin

Intervention vs. comparison (sample size; no. studies; reference)*	Outcome	Relative risk	Control group event rate, %	Absolute risk difference	Certainty
warfarin *vs. control* (2,313; 5; Aguilar 2005)	all-cause mortality	**RR 0.71 (95% CI 0.52 to 0.94)**	8.01%†	**-2.32% (95% CI -3.84% to -0.48%)**	High
	vascular death	RR 0.85 (95% CI 0.57 to 1.26)	4.40%†	-0.66% (95% CI -1.89% to 1.14%)	Moderate (imprecision)
apixaban *vs. warfarin* (18,201; 1; Bruins 2018)	all-cause mortality	RR 0.90 (95% CI 0.81 to 1.00)	7.37%†	-0.74% (95% CI -1.40% to 0%)	Low (high discontinuation rates and imprecision)§
	vascular death	not reported	n/a		
dabigatran 150 mg *vs. warfarin* (18,113; 1; Connolly 2009)	all-cause mortality	RR 0.88 (95% CI 0.77 to 1.00)	4.13%‡	-0.50% (95% CI -0.95% to 0%)	Low (lack of blinding and imprecision)§
	vascular death	**RR 0.85 (95% CI 0.72 to 0.99)**	2.69%‡	**-0.4% (95% CI -0.75% to -0.03%)**	Moderate (lack of blinding)
dabigatran 110 mg *vs. warfarin* (18,113; 1; Connolly 2009)	all-cause mortality	RR 0.91 (95% CI 0.8 to 1.03)	4.13%‡	-0.37% (95% CI -0.83% to 0.12%)	Low (lack of blinding and imprecision)§
	vascular death	RR 0.9 (95% CI 0.77 to 1.06)	2.69%‡	-0.27% (95% CI -0.62% to 0.16%)	Low (lack of blinding and imprecision)§
edoxaban 60 mg *vs. warfarin* (21,105; 1; Giugliano 2013)	all-cause mortality	RR 0.92 (95% CI 0.83 to 1.01)	4.35%‡	-0.35% (95% CI -0.74% to 0.04%)	Low (high discontinuation rates and

					imprecision)[§]
	cardiovascular death	**RR 0.85 (95% CI 0.77 to 0.97)**	3.17%[‡]	**-0.48% (95% CI -0.73% to -0.1%)**	Moderate (high discontinuation rates)
edoxaban 30 mg *vs. warfarin* (21,105; 1; Giugliano 2013)	all-cause mortality	**RR 0.87 (95% CI 0.79 to 0.96)**	4.35%[‡]	**-0.57% (95% CI -0.91% to -0.17%)**	Moderate (high discontinuation rates)
	cardiovascular death	**RR 0.85 (95% CI 0.76 to 0.96)**	3.17%[‡]	**-0.48% (95% CI -0.76% to -0.13%)**	Moderate (high discontinuation rates)
rivaroxaban *vs. warfarin* (14,264; 1; Bruins 2018)	all-cause mortality	RR 0.83 (95% CI 0.70 to 1.00)	3.53%[†]	-0.6% (95% CI -1.06% to 0%)	Low (high discontinuation rates and imprecision)[§]
	vascular death	RR 0.88 (0.72 to 1.08)	2.73%[†]	-0.33% (95% CI -0.76% to 0.22%)	Low (high discontinuation rates and imprecision)[§]

Statistically-significant effects are **bolded**.

[*] The number listed for sample size is the total number randomized. However, for dabigatran and edoxaban, the data come from 3-armed trials studying 2 different doses of the respective DOAC versus warfarin. The number in each group is as follows: dabigatran 150 mg (n = 6,076), dabigatran 110 mg (n = 6,015), warfarin (n = 6,022); edoxaban 60 mg (n = 7,035), edoxaban 30 mg (n = 7,034), warfarin (n = 7,036).

[†] These rates are over the full duration of follow-up for the respective intervention and comparison: warfarin vs. control, mean of 1.5 years; apixaban vs. warfarin, median of 1.8 years; rivaroxaban, median of 1.9 years. Therefore, the corresponding absolute risk difference estimates are for the same respective time period.

[‡] These rates are per year. Therefore, the corresponding absolute risk difference estimates are also per year.

[§] The threshold used to define certainty for these outcomes has an impact on the certainty rating. For the outcomes marked with an [§], the threshold used was the same as that used for all other outcomes, namely: "Is the medication *better than* warfarin?". Therefore, these outcomes were downgraded for imprecision, as the CI includes the possibility that there was either no benefit or no clinically-meaningful benefit compared to warfarin, or in some cases, the possibility of a worsening compared to warfarin that is of an uncertain clinical relevance (estimated absolute risk differences are in the table). If one instead used a threshold of "Is the medication *no worse than* warfarin?" all outcomes with an [§] may very well *not* be downgraded for imprecision (depending on what someone considers an acceptable threshold for noninferiority), which would then mean these outcomes would have Moderate certainty.

FAQ 4: What is my risk of major bleeding?

The one-year risk of a major bleeding event while taking warfarin is estimated via the HAS-BLED risk prediction model, as specified in Part 1 Scoping. Specifically, the estimated one-year risk presented here comes from Friberg 2012's large, prospective validation study, using a HAS-BLED score of 2 (the most common score in Friberg 2012) as an example score (as specified in Part 1 Scoping). This score corresponds to an estimated one-year risk of 1.9%.

To estimate the one-year risk of a major bleeding event while taking one of the direct oral anticoagulants (DOACs; apixaban, dabigatran, edoxaban, and rivaroxaban), the one-year risk while taking warfarin is adjusted by the relative risk data for the respective DOAC vs. warfarin. For example, the one-year risk of 1.9% while taking warfarin is multiplied by the relative risk of 0.70 for apixaban vs. warfarin to yield a point estimate of the one-year risk while taking apixaban; this process is repeated for the lower and upper bounds of the relative risk confidence interval for apixaban vs. warfarin.

Evidence Review Table – Apixaban, Dabigatran, Edoxaban, and Rivaroxaban

One-year risk of a major bleeding event when taking apixaban, dabigatran, edoxaban, or rivaroxaban

Medication (sample size; no. studies; reference)*	**Certainty**	**Relative risk (vs. warfarin)**	**Based on the estimated one-year risk of 1.9% for a major bleeding event while on warfarin with a HAS-BLED of 2, the one-year risk while taking the respective DOAC is estimated to be**
apixaban (18,201; 1; Bruins 2018)	Moderate (high discontinuation rates)	**RR 0.70 (95% CI 0.61 to 0.81)**	**1.33% (95% CI 1.16% to 1.54%)**
dabigatran 150 mg (18,113; 1; Connolly 2009)	Low (lack of blinding in warfarin group and imprecision)†	RR 0.94 (95% CI 0.82 to 1.08)	1.79% (95% CI 1.56% to 2.05%)
dabigatran 110 mg (18,113; 1; Connolly 2009)	Moderate (lack of blinding in warfarin group)	**RR 0.80 (95% CI 0.70 to 0.93)**	**1.52% (95% CI 1.33% to 1.77%)**
edoxaban 60 mg (21,105; 1; Giugliano 2013)	Moderate (high discontinuation rates)	**RR 0.80 (95% CI 0.71 to 0.91)**	**1.52% (95% CI 1.35% to 1.73%)**
edoxaban 30 mg (21,105; 1; Giugliano 2013)	Moderate (high discontinuation rates)	**RR 0.47 (95% CI 0.41 to 0.55)**	**0.89% (95% CI 0.78% to 1.05%)**
rivaroxaban (14,264; 1; Bruins 2018)	Low (high discontinuation rates and imprecision)†	RR 1.03 (95% CI 0.89 to 1.18)	1.96% (95% CI 1.69% to 2.24%)

Effects are **bolded** if statistically-significant compared to warfarin.

[*] The number listed for sample size is the total number randomized. However, for dabigatran and edoxaban, the data come from 3-armed trials studying 2 different doses of the respective DOAC versus warfarin. The number in each group is as follows: dabigatran 150 mg (n = 6,076), dabigatran 110 mg (n = 6,015), warfarin (n = 6,022); edoxaban 60 mg (n = 7,035), edoxaban 30 mg (n = 7,034), warfarin (n = 7,036).

[†] The threshold used to define certainty for these outcomes has an impact the certainty rating. For these outcomes, the threshold used was "Is the medication *better than* warfarin?" For this reason, these outcomes are downgraded for imprecision, as they include the possibility of both clinically-irrelevant benefit, no benefit, and a clinically-questionable degree of harm compared to warfarin. For instance, the upper bounds of the CIs for dabigatran 150 mg and rivaroxaban yield absolute risk *increases* in major bleeding compared to warfarin of approximately 0.15% and 0.34%, respectively. However, the vast majority of the CI suggests dabigatran 150 mg and rivaroxaban are at least no worse than warfarin and may confer some degree of risk reduction for the outcome of major bleeding. Therefore, if one were to instead use the threshold of "Is the medication *no worse than* warfarin?", the outcomes marked with a [†] may very well *not* be downgraded for imprecision (depending on what someone considers an acceptable threshold for noninferiority), which would then mean these outcomes would have Moderate certainty.

FAQ 5: Can the blood-thinning effect of the treatment be reversed?

Descriptive Evidence Review

Below, we have tabulated information on available options for reversal when reversal is deemed appropriate. However, the specifics of how to manage bleeding and whether/when and how to reverse an oral anticoagulant also depend on the clinical specifics of the situation and are not addressed in detail here, as this is beyond the specified scoping for this evidence report.

Anticoagulant	Can it be reversed?	Options for reversal
vitamin K antagonist	Yes	vitamin K[*], 4F-PCC[*]
apixaban	Yes/Not yet[†]	andexanet alfa[†], 4F-PCC[‡], FEIBA[‡], and can consider activated charcoal for known recent ingestion
dabigatran	Yes	idarucizumab[§], 4F-PCC (efficacy not well-established)[‡], FEIBA[‡], and can consider activated charcoal for known recent ingestion
edoxaban	Yes/Not yet[†]	andexanet alfa[†], 4F-PCC[‡], FEIBA[‡], and can consider activated charcoal for known recent ingestion
rivaroxaban	Yes/Not yet[†]	andexanet alfa[†], 4F-PCC[‡], FEIBA[‡], and can consider activated charcoal for known recent ingestion

Table based on Tomaselli 2017, Tornkvist 2018, and Verma 2018. 4F-PCC, 4-factor prothrombin complex concentrate; FEIBA, factor VIII inhibitor bypassing activity (an activated prothrombin complex concentrate [aPCC] and the only aPCC available in the United States)

[*] Vitamin K is a specific reversal agent for vitamin K antagonists, but since the effects of vitamin K are not immediate, 4F-PCC is typically also given when seeking to reverse vitamin K antagonists with vitamin K, because 4F-PCC contains the vitamin K-dependent factors II, VII, IX, and X and proteins C and S. If 4F-PCC is unavailable, Tomaselli 2017 recommends plasma.

[†] Although a specific reversal agent for factor Xa inhibitors (andexanet alfa) has been approved, widespread clinical availability is not yet the norm (Verma 2018), and for some factor Xa inhibitors, the reversal agent has not been officially approved by regulatory bodies (e.g., andexanet alfa is approved by the United States Food and Drug Administration, but only for apixaban and rivaroxaban; the Committee for Medicinal Products for Human Use of the European Medicines Agency is currently expected to render an opinion on andexanet alfa in late February 2019).

[‡] Reversal properties based on limited *in vitro* or healthy human *in vivo* experiments, and efficacy of 4F-PCC has only been discussed in case reports. Tomaselli 2017 considers aPCC/FEIBA to be a second-line option to 4F-PCC for apixaban, edoxaban, and rivaroxaban and an equally-acceptable option to 4F-PCC for dabigatran (both being second-line to idarucizumab).

[§] Specific reversal agent for dabigatran approved by the Food and Drug Administration and European Medicines Agency, brand name Praxbind®.

FAQ 6: What do I do if I need surgery or a procedure?

Descriptive Evidence Review

The approach to the patient on an oral anticoagulant who is in the perioperative or periprocedural period can be broadly classified into considerations for the direct oral anticoagulants (DOACs; apixaban, dabigatran, edoxaban, and rivaroxaban) and vitamin K antagonists (VKAs; warfarin or other coumarin derivatives or congeners). Within each classification, we have answered 4 key questions as presented in Doherty 2017: whether to interrupt oral anticoagulant therapy, when to interrupt oral anticoagulant therapy, whether to bridge, and how to restart oral anticoagulation. We have omitted specifics on how to bridge if bridging is pursued, as that is beyond the scope of this evidence review, but further details are provided in Doherty 2017. Doherty 2017 also provides an online appendix with common procedures and associated bleeding risk.

Direct oral anticoagulants

Whether to interrupt DOAC therapy

<table>
<tr><td>Patient has ≥1 increased-bleeding-risk feature*</td><td colspan="2">Patient has no increased-bleeding-risk features*</td></tr>
<tr><td rowspan="3">Interrupt DOAC therapy.
Proceed to “When to interrupt”.</td><td colspan="2">Assess the bleeding risk specific to the procedure</td></tr>
<tr><td>No clinically-important procedure-specific bleeding risk</td><td>Any other degree of procedure-specific bleeding risk (i.e., low, intermediate, high, or uncertain risk)</td></tr>
<tr><td>Perform the procedure without interrupting the DOAC, but time it at a DOAC interval trough.</td><td>Interrupt DOAC therapy.
Proceed to “When to interrupt”.</td></tr>
</table>

* Doherty 2017 suggests any of the following constitutes an increased risk: major bleed or intracranial hemorrhage within the past 3 months, platelet abnormality (quantitative or qualitative, including concomitant aspirin use), bleeding during previous bridging. We note that clinical judgment may also include other factors.

When to interrupt DOAC therapy

This consideration centers on 4 variables:

- whether the patient is at increased bleeding risk (see “Whether to interrupt”)
- whether the DOAC is a direct thrombin inhibitor (dabigatran) or factor Xa inhibitor (apixaban, edoxaban, or rivaroxaban)
- the patient’s creatinine clearance
- the bleeding risk specific to the procedure.

The table below captures suggested actions for patients ***without*** an increased bleeding risk. The withholding durations are based on the estimated half-life withholding times of 2 to 3 half-lives for low procedural bleeding risk and 4 to 5 half-lives for intermediate, high, or uncertain procedural bleeding risk. For patients ***with*** increased bleeding risk, there are insufficient data on best practices, and it is recommended that

DOAC therapy be interrupted at least as long as determined by creatinine clearance as documented in the table below, and possibly longer, but clinicians must also use clinical judgment.

For patients *without* an increased bleeding risk: Estimated drug half-lives and recommended duration of discontinuation prior to procedure based on creatinine clearance and procedural bleeding risk

	dabigatran					apixaban, edoxaban, or rivaroxaban		
CrCl, mL/min	≥80	50-79	30-49	15-29	<15*	≥30	15-29	<15*
Half-life, h	13	15	18	27	30	6-15	apixaban: 17 edoxaban: 17 rivaroxaban: 9	apixaban: 17 edoxaban: 10 to 17 rivaroxaban: 13
Procedural bleeding risk								
Low†	≥24 h	≥36 h	≥48 h	≥72 h	No data; consider measuring dTT and/or withholding ≥96 h	≥24 h	≥36 h	No data; consider measuring agent-specific anti Xa level and/or withholding ≥48 h
Intermediate, high, or uncertain†	≥48 h	≥72 h	≥96 h	≥120 h	No data; consider measuring dTT	≥48 h	No data; consider measuring agent-specific anti Xa level and/or withholding ≥72 h	

CrCl, creatinine clearance; dTT, direct thrombin time; h, hours; mL/min, milliliters per minute

* Off-dialysis values reported for half-life; on-dialysis values not reported

† Durations shown are the recommended duration of discontinuation prior to the procedure based on the corresponding CrCl

For patients *with* increased bleeding risk: There are insufficient data on best practices. It is recommended that DOAC therapy be interrupted at least as long as determined by creatinine clearance as documented in the table above, and possibly longer. Use clinical judgment.

Whether to bridge

Bridging is not indicated with DOAC therapy. This is due to their short half-lives (compared to VKAs). Figure 4 of Doherty 2017 specifically says bridging is not indicated, and this is consistent with clinical practice and the pharmacokinetic and -dynamic profiles of the DOACs. However, Doherty 2017 also reasonably allows for some ambiguity in the text of their guidance, and they also address possible delays in restarting the DOAC after the procedure, which may lead to consideration of a short-term parenteral anticoagulant being administered:

> *Given the short-half lives of DOACs, bridging with a parenteral agent is rarely, if ever, needed prior to procedures. Reinitiation of these agents after the procedure, however, may need to be delayed owing to the risk of postprocedural bleeding. Reinitiation might also be delayed depending upon: 1) the need for additional procedures; and/or 2) the patient's ability to tolerate oral medications. In these latter 2 circumstances, a short-acting parenteral anticoagulant (e.g., unfractionated heparin [UFH]) may be needed either between procedures*

or post-procedure, when thrombotic risk remains high. Depending on the indication (e.g., venous thromboembolism prophylaxis), a prophylactic dose of UFH or LMWH may be sufficient. These are very specific scenarios that are uncommon in routine clinical practice.

How to restart

Cardiac valve surgery is not considered here, because this would be an indication for VKA therapy; thus, restarting anticoagulation here would fall under the VKA pathway.

Otherwise, the recommended actions are captured in the table below.

Restarting DOAC therapy after a procedure in a patient with complete hemostasis, no bleeding complications, no high-bleed-risk features, and no potential for a bleed at a catastrophic location (e.g., intracranial, intraspinal)*

Patient ***cannot*** tolerate oral medication		Patient ***can*** tolerate oral medication	
High postprocedural bleeding risk	***Low*** postprocedural bleeding risk	***High*** postprocedural bleeding risk	***Low*** postprocedural bleeding risk
Consider parenteral anticoagulation until oral medications are possible. Start parenteral agent within 48-72 hours following the procedure.† When tolerating oral medications, convert from parenteral agent to DOAC.	Consider parenteral anticoagulation until oral medications are possible. Start parenteral agent within 24 hours following the procedure.† When tolerating oral medications, convert from parenteral agent to DOAC.	Reasonable to reinitiate DOAC 48-72 hours after the procedure.†‡	Reasonable to reinitiate DOAC 24 hours after the procedure.† Consider using a reduced dose on the evening after the procedure.‡

* If any of these are present, then use clinical judgment in cooperation with the managing team and the proceduralist.
† At a dose based on postprocedural renal function
‡ In cooperation with the managing team and proceduralist

Vitamin K antagonists

Whether to interrupt VKA therapy

First, assess whether the patient has an increased bleeding risk. Doherty 2017 suggests any 1 of the following constitutes an increased risk (though we note clinical judgment may include other factors): major bleed or intracranial hemorrhage within the past 3 months, platelet abnormality (quantitative or qualitative, including concomitant aspirin use), INR above therapeutic range, or bleeding during previous bridging or similar procedure

- if yes, assess procedural bleed risk
    - if procedural bleed risk is either not clinically important or low
        - insufficient data on best practices; likely interrupt but consult with proceduralist

            - using clinical judgment, is there persistent concern for bleeding?
                - if yes, interrupt VKA therapy
                - if no, do not interrupt VKA therapy
    - if procedural bleed risk is intermediate, high, or uncertain, interrupt VKAs
- if no, assess procedural bleed risk
    - if ether not clinically important or low, do not interrupt VKA therapy
    - if intermediate or high, interrupt VKA therapy
    - if uncertain
        - insufficient data on best practices; likely interrupt but consult with proceduralist
            - using clinical judgment, is there persistent concern for bleeding?
                - if yes, interrupt VKA therapy
                - if no, do not interrupt VKA therapy

When to interrupt VKA therapy

Once the decision to interrupt has been made, when to interrupt is determined by INR measurement 5-7 days prior to procedure

- if INR at goal level (i.e., 2.0 to 2.5 or 2.0 to 3.0) or supratherapeutic
    - discontinue 5 days (at goal) or ≥5 days (supratherapeutic) prior to procedure depending on
        - current INR
        - time to procedure
        - desired INR for procedure
    - recheck INR 24 hours prior to procedure
- if INR is subtherapeutic
    - discontinue 3-4 days prior to procedure
    - recheck INR 24 hours prior to procedure if normal INR is desired

Whether to bridge

Whether to bridge ultimately amounts to balancing increased risk of a thromboembolic event from being off anticoagulation with the increased risk of a major bleeding event in the periprocedural period. Part of this assessment for the patient with nonvalvular atrial fibrillation will include his/her predicted thromboembolic risk as assessed via CHA2DS2-VASc score, but other factors may be considered as well (e.g., the thromboembolic risk from the surgery/procedure itself).

- assess patient thrombotic risk definitions (as defined by Doherty 2017)
    - “low” if CHA_2DS_2-VASc score of 1-4 (annualized stroke risk <5%) and no prior thromboembolic event

    - "moderate" if CHA_2DS_2-VASc score of 5-6 (annualized stroke risk 5%-10%) or prior thromboembolic event >3 months previously
    - "high" if CHA_2DS_2-VASc score of 7 or more (annualized stroke risk >10%) or prior thromboembolic event ≤3 months previously
- assess patient bleed risk, considered increased if ≥1 of following
    - major bleed or intracranial hemorrhage <3 months
    - quantitative or qualitative platelet abnormality including aspirin use
    - INR above therapeutic range
    - prior bleed from previous bridging
- outside of instances where there is either a clear indication or contraindication to bridging, the choice to bridge is based on assessment of patient thrombotic risk and patient bleed risk to determine whether the balance of benefits and harms favors bridging or not bridging; Doherty 2017 provides suggestions for situations where the decision is "likely bridge" or "likely do not bridge", but then ends with "use clinical judgement"

How to restart VKA therapy

Assess whether complete hemostasis was achieved, with no bleeding complications, no high-risk features of patient, and no potentially catastrophic bleed location (e.g., intracranial, intraspinal).

- if no, consider delaying restarting anticoagulation; use clinical judgment in cooperation with managing team and proceduralist
- if yes, assess whether plan or indication to give parenteral agent following procedure
    - if no, start VKA within 24 hours in cooperation with managing team and proceduralist
    - if yes, assess postprocedural bleed risk
        - if high postprocedural bleed risk
            - start VKA within 24 hours
            - restart parenteral agent if applicable 48-72 hours after procedure
            - discontinue parenteral agent when INR reaches 2
        - if low postprocedural bleed risk
            - start VKA within 24 hours
            - restart parenteral agent if applicable ≤24 hours after procedure
            - discontinue parenteral agent when INR reaches 2

Medical therapy (FAQ7b)

Descriptive Overview

You may need to have your rate or rhythm control medication adjusted over time to maintain control of your atrial fibrillation.

Part 5 - Evidence Synthesis

Methods

Evidence synthesis process

Synthesis methods will be based on the most appropriate methods matching the available evidence. We will systematically consider synthesis methods with the following questions:

Is it useful and appropriate to present the synthesis of evidence results as a combined, single result as the best representation of the body of evidence?

State "Yes" or "No". Provide justification if "No".

If "Yes", what method is the best approach?

Pick one of the following and justify:

(1) meta-analysis already done

(2) meta-analysis created from the evidence results

(3) median of sufficiently-valid results, stating cutoff for validity

(4) median of all results

If "No", what method is best to represent the evidence synthesis?

Pick one of the following and justify:

(1) range of all results

(2) range of sufficiently valid results

(3) descriptive summary without quantitative representation (e.g., consistency in direction, but inconsistency in magnitude)

(4) statement of inconsistency too limiting for single synthesized conclusion

Where evidence is very limited or the FAQ is for descriptive summary, such that summary text was provided instead of Evidence Review Tables, the Descriptive Evidence Summary will be noted.

Results

FAQ 1: What does the treatment involve?

Pre-Synthesis Efforts: Not applicable (descriptive summary provided)

For all options, doctors may change dosing or monitoring for individual patients based on other conditions or medications. For all options, heavy alcohol use is not recommended; it may increase risk of bleeding. For all options, the medicine is a strong blood thinner that makes it less likely for blood clots to form.

Vitamin K antagonists (FAQ1a)

Descriptive Evidence Summary

You will take a pill once a day, with or without food. You will need regular blood tests to check how thin your blood is. You may need to change your diet to keep a similar amount of vitamin K each day.

Apixaban (FAQ1b)

Descriptive Evidence Summary

You will take a pill twice a day, with or without food. You do not need blood tests to check how thin your blood is. You will have blood tests to check your kidneys to determine the right dose.

Dabigatran (FAQ1c)

Descriptive Evidence Summary

You will take a pill twice a day, with or without food. You do not need blood tests to check how thin your blood is. You will have blood tests to check your kidneys to determine the right dose.

Edoxaban (FAQ1d)

Descriptive Evidence Summary

You will take a pill once a day, with or after food. You do not need blood tests to check how thin your blood is. You will have blood tests to check your kidneys to determine the right dose.

Rivaroxaban (FAQ1e)

Descriptive Evidence Summary

You will take a pill once a day, with or after food. You do not need blood tests to check how thin your blood is. You will have blood tests to check your kidneys to determine the right dose.

FAQ 2: What is my risk of a thromboembolic/ischemic stroke?

Pre-Synthesis Efforts:

Part 2 Search:

	Number of articles evaluated	**Number of unique articles selected for evaluation**
First-round (DynaMed Plus)	113	11 (Aguilar 2005, Bruins 2018, Cohen 2016, Connolly 2009, European Medicines Agency 2016, Giugliano 2013, Granger 2011, NICE 2014, Patel 2011, Salazar 2014, Seife 2015)
Second-round (Systematic review searches)	0	0
Third-round (Original study tracing)	11	0
Fourth-round (Original article searches)	149	0

Part 3 Critical Appraisal (evidence evaluated for FAQ2):

Certainty rating	**Systematic reviews**	**Randomized trials**	**Other article types**
High	Aguilar 2005 (warfarin, 5 trials, n = 2,313)		
Moderate		Connolly 2009 (dabigatran, n = 18,113)	
Low	Bruins 2018 (apixaban, 1 trial [Granger 2011], n = 18,201; rivaroxaban, 1 trial [Patel 2011], n = 14,264)	Giugliano 2013 (edoxaban, n = 21,105)	
Very low			
Unusable	Salazar 2014		
Not applicable	NICE 2014	Granger 2011 (captured by Bruins 2018), Patel 2011 (captured by Bruins 2018)	Cohen 2016, European Medicines Agency 2016, Seife 2015

Part 4 Results for FAQ2:

- Vitamin K antagonists (phenprocoumon, warfarin, or other coumarin derivatives or congeners) reduce the risk of thromboembolic/ischemic stroke compared to no treatment with relative risk 0.35 (95% CI 0.24 to 0.54). (Aguilar 2005, High certainty)
- Apixaban might be as effective as warfarin for reducing the risk of thromboembolic/ischemic stroke with relative risk 0.92 (95% CI 0.75 to 1.14). (Bruins 2018, Low certainty)
- Dabigatran 150 mg may be as or more effective than warfarin for reducing the risk of thromboembolic/ischemic stroke with relative risk 0.76 (95% CI 0.59 to 0.97). (Connolly 2009, Moderate certainty). Dabigatran 150 mg dosing is reported here. See Part 4 for dabigatran 110 mg dosing.
- Edoxaban 60 mg might be as effective as warfarin for reducing the risk of thromboembolic/ischemic stroke with relative risk 1.00 (95% CI 0.83 to 1.19). (Giugliano 2013, Low certainty). Edoxaban 60 mg dosing is reported here. See Part 4 for edoxaban 30 mg dosing.
- Rivaroxaban might be as effective as warfarin for reducing the risk of thromboembolic/ischemic stroke with relative risk 0.93 (95% CI 0.74 to 1.16). (Bruins 2018, Low certainty)

Evidence Synthesis Process for FAQ2

Is it useful and appropriate to present the synthesis of evidence results as a combined, single result as the best representation of the body of evidence?

Yes.

If "Yes", what method is the best approach?

(1) meta-analysis already done

Results from a meta-analysis of randomized, controlled trials (for warfarin vs. control) and from large randomized, controlled trials (for other drugs vs. warfarin) provide relative risk estimates representing the best estimates of effect from the body of evidence.

Because the baseline risk (risk with no treatment) is estimated by the CHA_2DS_2-VASc score, answers are provided here for patients with a CHA_2DS_2-VASc score of 2 (a common threshold where guidelines begin recommending oral anticoagulation) and a score of 4 (the most common score in Friberg 2012's large, prospective validation study), as noted in Part 1 Scoping.

Without treatment, patients with CHA_2DS_2-VASc score of 2 have an estimated 2.5% risk of thromboembolic/ischemic stroke within 1 year.

Without treatment, patients with CHA_2DS_2-VASc score of 4 have an estimated 5.5% risk of thromboembolic/ischemic stroke within 1 year.

Vitamin K antagonists (FAQ2a)

Vitamin K antagonists (phenprocoumon, warfarin, or other coumarin derivatives or congeners) reduce the risk of thromboembolic/ischemic stroke compared to no treatment with relative risk 0.35 (95% CI 0.24 to 0.54). (Aguilar 2005, High certainty)

With vitamin K antagonists, patients with CHA_2DS_2-VASc score of 2 have a 0.88% risk (95% CI 0.6% to 1.35%) of thromboembolic/ischemic stroke within 1 year.

With vitamin K antagonists, patients with CHA_2DS_2-VASc score of 4 have a 1.93% (95% CI 1.32% to 2.97%) risk of thromboembolic/ischemic stroke within 1 year.

For the estimates of thromboembolic/ischemic stroke for a patient with a CHA_2DS_2-VASc score of 2 or 4 taking a direct oral anticoagulant (DOAC; apixaban, dabigatran, edoxaban, or rivaroxaban), we use the above rates of thromboembolic/ischemic stroke while taking a vitamin K antagonist (i.e., 0.88% and 1.93%) as the "control group" risk for each of the respective DOACs. Part 4 has additional detail.

Apixaban (FAQ2b)

Apixaban might be as effective as warfarin for reducing the risk of thromboembolic/ischemic stroke with relative risk 0.92 (95% CI 0.75 to 1.14). (Bruins 2018, Low certainty)

With apixaban, patients with CHA_2DS_2-VASc score of 2 have a 0.81% risk (95% CI 0.66% to 1%) of thromboembolic/ischemic stroke within 1 year.

With apixaban, patients with CHA_2DS_2-VASc score of 4 have a 1.78% risk (95% CI 1.45% to 2.2%) of thromboembolic/ischemic stroke within 1 year.

Dabigatran (FAQ2c)

Dabigatran 150 mg dosing is reported here. See Part 4 for dabigatran 110 mg dosing.

Dabigatran 150 mg may be as or more effective than warfarin for reducing the risk of thromboembolic/ischemic stroke with relative risk 0.76 (95% CI 0.59 to 0.97). (Connolly 2009, Moderate certainty)

With dabigatran, patients with CHA_2DS_2-VASc score of 2 have a 0.67% risk (95% CI 0.52% to 0.85%) of thromboembolic/ischemic stroke within 1 year.

With dabigatran, patients with CHA_2DS_2-VASc score of 4 have a 1.47% risk (95% CI 1.14% to 1.87%) of thromboembolic/ischemic stroke within 1 year.

Edoxaban (FAQ2d)

Edoxaban 60 mg dosing is reported here. See Part 4 for edoxaban 30 mg dosing.

Edoxaban 60 mg might be as effective as warfarin for reducing the risk of thromboembolic/ischemic stroke with relative risk 1.00 (95% CI 0.83 to 1.19). (Giugliano 2013, Low certainty)

With edoxaban, patients with CHA_2DS_2-VASc score of 2 have a 0.88% risk (95% CI 0.73% to 1.05%) of thromboembolic/ischemic stroke within 1 year.

With edoxaban, patients with CHA_2DS_2-VASc score of 4 have a 1.93% risk (95% CI 1.6% to 2.3%) of thromboembolic/ischemic stroke within 1 year.

Rivaroxaban (FAQ2e)

Rivaroxaban might be as effective as warfarin for reducing the risk of thromboembolic/ischemic stroke with relative risk 0.93 (95% CI 0.74 to 1.16). (Bruins 2018, Low certainty)

With rivaroxaban, patients with CHA_2DS_2-VASc score of 2 have a 0.82% risk (95% CI 0.65% to 1.02%) of thromboembolic/ischemic stroke within 1 year.

With rivaroxaban, patients with CHA_2DS_2-VASc score of 4 have a 1.79% risk (95% CI 1.43% to 2.24%) of thromboembolic/ischemic stroke within 1 year.

FAQ 3: Will I live longer or avoid dying from a specific cause because of treatment?

Pre-Synthesis Efforts:

Part 2 Search:

	Number of articles evaluated	Number of unique articles selected for evaluation
First-round (DynaMed Plus)	113	11 (Aguilar 2005, Bruins 2018, Cohen 2016, Connolly 2009, European Medicines Agency 2016, Giugliano 2013, Granger 2011, NICE 2014, Patel 2011, Salazar 2014, Seife 2015)
Second-round (Systematic review searches)	0	0
Third-round (Original study tracing)	11	0
Fourth-round (Original article searches)	149	0

Part 3 Critical Appraisal (evidence evaluated for all-cause mortality for FAQ3):

Certainty rating	Systematic reviews	Randomized trials	Other article types
High	Aguilar 2005 (warfarin, 5 trials, n = 2,313)		
Moderate			
Low	Bruins 2018 (apixaban, 1 trial [Granger 2011], n = 18,201; rivaroxaban, 1 trial [Patel 2011], n = 14,264)	Connolly 2009 (dabigatran, n = 18,113), Giugliano 2013 (edoxaban, n = 21,105)	
Very low			
Unusable	Salazar 2014		
Not applicable	NICE 2014	Granger 2011 (captured by Bruins 2018), Patel 2011 (captured by Bruins 2018)	Cohen 2016, European Medicines Agency 2016, Seife 2015

Part 3 Critical Appraisal (evidence evaluated for cause-specific mortality for FAQ3):

Certainty rating	Systematic reviews	Randomized trials	Other article types
High			
Moderate	Aguilar 2005 (warfarin, 5 trials, n = 2,313)	Connolly 2009 (dabigatran, n = 18,113), Giugliano 2013 (edoxaban, n = 21,105)	
Low	Bruins 2018 (rivaroxaban, 1 trial [Patel 2011], n = 14,264)		
Very low			
Unusable	Salazar 2014		
Not applicable	NICE 2014	Patel 2011 (captured by Bruins 2018)	Cohen 2016, European Medicines Agency 2016, Seife 2015

Part 4 Results for FAQ3:

- comparing warfarin vs. no anticoagulants
  - reduced all-cause mortality (RR 0.71, 95% CI 0.52 to 0.94) (Aguilar 2005, High certainty)
  - no significant difference in vascular death (RR 0.85, 95% CI 0.57 to 1.26) (Aguilar 2005, Moderate certainty)
- comparing apixaban vs. warfarin
  - similar or reduced all-cause mortality (RR 0.9, 95% CI 0.81 to 1.00) (Bruins 2018, Low certainty)
  - Cause-specific mortality not reported
- comparing dabigatran 150 mg vs. warfarin
  - similar or reduced all-cause mortality (RR 0.88, 95% CI 0.77 to 1.00) (Connolly 2009, Low certainty)
  - reduced vascular death (RR 0.85, 95% CI 0.72 to 0.99) (Connolly 2009, Moderate certainty)
- comparing edoxaban 60 mg vs. warfarin
  - similar or reduced all-cause mortality (RR 0.92, 95% CI 0.83 to 1.01) (Giugliano 2013, Low certainty)
  - reduced cardiovascular death (RR 0.85, 95% CI 0.77 to 0.97) (Giugliano 2013, Moderate certainty)
- comparing rivaroxaban vs. warfarin
  - similar or reduced all-cause mortality (RR 0.83, 95% CI 0.7 to 1.00) (Bruins 2018, Low certainty)

- no significant difference in vascular death (RR 0.88, 95% CI 0.72 to 1.08) (Bruins 2018, Low certainty)

Evidence Synthesis Process for FAQ3

Is it useful and appropriate to present the synthesis of evidence results as a combined, single result as the best representation of the body of evidence?

Yes.

If "Yes", what method is the best approach?

(1) meta-analysis already done

Results from a meta-analysis of randomized, controlled trials (for warfarin vs. control) and from large randomized, controlled trials (for other drugs vs. warfarin) provide relative risk estimates representing the best estimates of effect from the body of evidence.

Vitamin K antagonists (FAQ3a)

Vitamin K antagonists reduce all-cause mortality compared to not using anticoagulants in people with nonvalvular atrial fibrillation, with a relative risk of 0.71 (95% CI 0.52 to 0.94) and a rate of all-cause mortality in the control group of 8.01% over a mean follow-up of 1.5 years. (Aguilar 2005, High certainty) The corresponding absolute estimate for all-cause mortality with vitamin K antagonists would be 5.7% (95% CI 4.2% to 7.5%).

Vitamin K antagonists have an unclear effect on vascular mortality compared to not using anticoagulants in people with nonvalvular atrial fibrillation, with a relative risk of 0.85 (95% CI 0.57 to 1.26) and a rate of vascular death in the control group of 4.40%. (Aguilar 2005, Moderate certainty) The corresponding absolute estimate for vascular mortality with vitamin K antagonists would be 3.7% (95% CI 2.5% to 5.5%).

There is lower certainty in effect estimates for vascular mortality, and the effect on vascular mortality does not explain most of the effect on all-cause mortality. It is thus unclear how the effect on all-cause mortality is realized, as vascular death is presumably the primary cause-specific mortality affected by vitamin K antagonists.

Vitamin K antagonists reduce all-cause mortality compared to not using anticoagulants in people with nonvalvular atrial fibrillation. (Aguilar 2005, High certainty) With a relative risk of 0.71 (95% CI 0.52 to 0.94), this means if 80 out of 1000 people would die without anticoagulant treatment, 57 out of 1000 people would die with vitamin K antagonists, and 23 out of 1000 people would avoid death because of the treatment (95% CI 5 to 38 deaths avoided out of 1000 people). The exact cause of death is not clear.

For the estimates for all-cause and vascular/cardiovascular mortality for the direct oral anticoagulants (DOACs; apixaban, dabigatran, edoxaban, or rivaroxaban), we use the point estimates for all-cause mortality and vascular mortality while taking a vitamin K antagonist (i.e., 5.7% and 3.7%, respectively, or 57 and 37 out of 1000, respectively) as the "control group" risk, and we assume vascular mortality and

cardiovascular mortality are similar enough to treat as interchangeable for purposes of estimating absolute effects.

Apixaban (FAQ3b)

Apixaban may be associated with similar or lower all-cause mortality compared to vitamin K antagonists in people with nonvalvular atrial fibrillation, with a relative risk of 0.9 (95% CI 0.81 to 1.00). (Bruins 2018, Low certainty) The corresponding absolute estimate for all-cause mortality with apixaban would be 5.1% (95% CI 4.6% to 5.7%).

Data for cause-specific mortality are not reported by Bruins 2018.

Apixaban may be associated with similar or lower all-cause mortality compared to vitamin K antagonists in people with nonvalvular atrial fibrillation. (Bruins 2018, Low certainty) With a relative risk of 0.9 (95% CI 0.81 to 1.00), this means if 57 out of 1000 people would die with vitamin K antagonists, 51 out of 1000 people would die with apixaban, and 6 out of 1000 people would avoid death because of apixaban (95% CI 0 to 11 deaths avoided). The exact cause of death is not clear.

Dabigatran (FAQ3c)

Dabigatran 150 mg dosing is reported here. See Part 4 for dabigatran 110 mg dosing.

Dabigatran 150 mg may be associated with similar or lower all-cause mortality compared to vitamin K antagonists in people with nonvalvular atrial fibrillation, with a relative risk of 0.88 (95% CI 0.77 to 1.00). (Connolly 2009, Low certainty) The corresponding absolute estimate for all-cause mortality with dabigatran would be 5.0% (95% CI 4.4% to 5.7%).

Dabigatran 150 mg may be associated with a lower rate of vascular death compared to vitamin K antagonists in people with nonvalvular atrial fibrillation, with a relative risk of 0.85 (95% CI 0.72 to 0.99). (Connolly 2009, Moderate certainty) The corresponding absolute estimate for vascular mortality with dabigatran would be 3.1% (95% CI 2.7% to 3.7%).

Dabigatran may be associated with similar or lower all-cause mortality compared to vitamin K antagonists in people with nonvalvular atrial fibrillation. (Connolly 2009, Low certainty) With a relative risk of 0.88 (95% CI 0.77 to 1.00), this means if 57 out of 1000 people would die with vitamin K antagonists, 50 out of 1000 people would die with dabigatran 150 mg, and 7 out of 1000 people would avoid death because of dabigatran 150 mg (95% CI, 0 to 13 deaths avoided). This appears to be mainly due to a lower rate of vascular death (Connolly 2009, Moderate certainty), but rates of specific causes of vascular death were not reported.

Edoxaban (FAQ3d)

Edoxaban 60 mg dosing is reported here. See Part 4 for edoxaban 30 mg dosing.

Edoxaban 60 mg may be associated with similar or lower all-cause mortality compared to vitamin K antagonists in people with nonvalvular atrial fibrillation, with a relative risk of 0.92 (95% CI 0.83 to 1.01). (Giugliano 2013, Low certainty) The corresponding absolute estimate for all-cause mortality with edoxaban would be 5.2% (95% CI 4.7% to 5.8%).

Edoxaban 60 mg may be associated with a lower rate of cardiovascular death compared to vitamin K antagonists in people with nonvalvular atrial fibrillation, with a relative risk of 0.85 (95% CI 0.77 to 0.97). (Giugliano 2013, Moderate certainty) The corresponding absolute estimate for cardiovascular mortality with edoxaban would be 3.1% (95% CI 2.8% to 3.6%).

Edoxaban 60 mg may be associated with similar or lower all-cause mortality compared to vitamin K antagonists in people with nonvalvular atrial fibrillation. (Giugliano 2013, Low certainty) With a relative risk of 0.92 (95% CI 0.83 to 1.01), this means if 57 out of 1000 people would die with vitamin K antagonists, 52 out of 1000 people would die with edoxaban 60 mg, and 5 out of 1000 people would avoid death because of edoxaban 60 mg (95% CI 10 deaths *avoided* to 1 death *caused*). This appears to be mainly due to a lower rate of vascular death (Giugliano 2013, Moderate certainty), but rates of specific causes of cardiovascular death other than fatal stroke were not reported, and the effect on fatal stroke was not significant.

Rivaroxaban (FAQ3e)

Rivaroxaban may be associated with similar or lower all-cause mortality compared to vitamin K antagonists in people with nonvalvular atrial fibrillation, with a relative risk of 0.83 (95% CI 0.7 to 1.00). (Bruins 2018, Low certainty) The corresponding absolute estimate for all-cause mortality with rivaroxaban would be 4.7% (95% CI 4.0% to 5.7%).

Rivaroxaban may be associated with lower, similar, or slightly worse rates of vascular death compared to vitamin K antagonists in people with nonvalvular atrial fibrillation, with a relative risk of 0.88 (95% CI 0.72 to 1.08). (Bruins 2018, Low certainty) The corresponding absolute estimate for vascular mortality with rivaroxaban would be 3.3% (95% CI 2.7% to 4.0%).

The differential effect of rivaroxaban on vascular mortality is unclear, so it is unclear how much this contributes to the effect on all-cause mortality.

Rivaroxaban may be associated with similar or lower all-cause mortality compared to vitamin K antagonists in people with nonvalvular atrial fibrillation. (Bruins 2018, Low certainty) With a relative risk of 0.83 (95% CI 0.7 to 1.00), this means if 57 out of 1000 people would die with vitamin K antagonists, 47 out of 1000 people would die with rivaroxaban, and 10 out of 1000 people would avoid death because of choosing rivaroxaban (95% CI 0 to 17 deaths avoided). The exact cause of death is not clear.

FAQ 4: What is my risk of major bleeding?

Pre-Synthesis Efforts:

Part 2 Search:

	Number of articles evaluated	**Number of unique articles selected for evaluation**
First-round (DynaMed Plus)	113	10 (Bruins 2018, Cohen 2016, Connolly 2009, European Medicines Agency 2016, Giugliano 2013, Granger 2011, NICE 2014, Patel 2011, Salazar 2014, Seife 2015)
Second-round (Systematic review searches)	0	0
Third-round (Original study tracing)	11	0
Fourth-round (Original article searches)	93	0

Part 3 Critical Appraisal (evidence evaluated for FAQ4):

Certainty rating	**Systematic reviews**	**Randomized trials**	**Other article types**
High			
Moderate	Bruins 2018 (apixaban, 1 trial [Granger 2011], n = 18,201)	Giugliano 2013 (edoxaban, n = 21,105)	
Low	Bruins 2018 (rivaroxaban, 1 trial [Patel 2011], n = 14,264)	Connolly 2009 (dabigatran, n = 18,113)	
Very low			
Unusable	Salazar 2014		
Not applicable	NICE 2014	Granger 2011 (captured by Bruins 2018), Patel 2011 (captured by Bruins 2018)	Cohen 2016, European Medicines Agency 2016, Seife 2015

Part 4 Results for FAQ4:

- One-year risk of major bleeding on vitamin K antagonists is estimated at 1.9% with the HAS-BLED score of 2.
- Apixaban appears to have a lower risk for major bleeding compared to warfarin with relative risk 0.7 (95% CI 0.61 to 0.81). (Bruins 2018, Moderate certainty)
- Dabigatran 150 mg might have a similar risk for major bleeding compared to warfarin with relative risk 0.94 (95% CI 0.82 to 1.08). (Connolly 2009, Low certainty)
- Edoxaban 60 mg appears to have a lower risk for major bleeding compared to warfarin with relative risk 0.80 (95% CI 0.71 to 0.91). (Giugliano 2013, Moderate certainty)
- Rivaroxaban might have a similar risk for major bleeding compared to warfarin with relative risk 1.03 (95% CI 0.89 to 1.18). (Bruins 2018, Low certainty)

Evidence Synthesis Process for FAQ4

Is it useful and appropriate to present the synthesis of evidence results as a combined, single result as the best representation of the body of evidence?

Yes.

If "Yes", what method is the best approach?

(1) meta-analysis already done

The risk of major bleeding on vitamin K antagonists is estimated with the HAS-BLED score. Results from large randomized, controlled trials (for other drugs vs. warfarin) provide relative risk estimates representing the best estimate of effect from the body of evidence.

Vitamin K antagonists (FAQ4a)

Because the risk with vitamin K antagonists is estimated with the HAS-BLED score, answers are provided here for patients with a HAS-BLED score of 2 (the most common score in Friberg 2012's large prospective validation study), as noted in Part 1 Scoping.

With vitamin K antagonists, patients with HAS-BLED score of 2 have a one-year risk of major bleeding of 1.9%.

For the estimates for major bleeding for the direct oral anticoagulants (DOACs; apixaban, dabigatran, edoxaban, or rivaroxaban), we use the above rate of major bleeding while taking a vitamin K antagonist (i.e., 1.9%) as the "control group" risk.

Apixaban (FAQ4b)

Apixaban appears to have a lower risk for major bleeding compared to warfarin with relative risk 0.7 (95% CI 0.61 to 0.81). (Bruins 2018, Moderate certainty)

With apixaban, patients with HAS-BLED score of 2 have a one-year risk of major bleeding of 1.33% (95% CI 1.16% to 1.54%).

Dabigatran (FAQ4c)

Dabigatran 150 mg dosing is reported here. See Part 4 for dabigatran 110 mg dosing.

Dabigatran 150 mg might have a similar risk for major bleeding compared to warfarin with relative risk 0.94 (95% CI 0.82 to 1.08). (Connolly 2009, Low certainty)

With dabigatran 150 mg, patients with HAS-BLED score of 2 have a one-year risk of major bleeding of 1.79% (95% CI 1.56% to 2.05%).

Edoxaban (FAQ4d)

Edoxaban 60 mg dosing is reported here. See Part 4 for edoxaban 30 mg dosing.

Edoxaban 60 mg appears to have a lower risk for major bleeding compared to warfarin with relative risk 0.80 (95% CI 0.71 to 0.91). (Giugliano 2013, Moderate certainty)

With edoxaban 60 mg, patients with HAS-BLED score of 2 have a one-year risk of major bleeding of 1.52% (95% CI 1.35% to 1.73%).

Rivaroxaban (FAQ4e)

Rivaroxaban might have a similar risk for major bleeding compared to warfarin with relative risk 1.03 (95% CI 0.89 to 1.18). (Bruins 2018, Low certainty)

With rivaroxaban, patients with HAS-BLED score of 2 have a one-year risk of major bleeding of 1.96% (95% CI 1.69% to 2.24%).

FAQ 5: Can the blood-thinning effect of the treatment be reversed?

Pre-Synthesis Efforts: Not applicable (descriptive summary provided)

Additional detail regarding management of reversal with non-specific agents is noted in Part 4, compiled from Tomaselli 2017, Tornkvist 2018, and Verma 2018.

Vitamin K antagonists (FAQ5a)

Descriptive Evidence Summary

Yes. Vitamin K is a specific reversal agent. Because vitamin K takes time to work, 4-factor prothrombin complex concentrate may also be used to augment the effect.

Apixaban (FAQ5b)

Descriptive Evidence Summary

Not yet but this may change with new drugs. Andexanet alfa is a reversal agent that is undergoing evaluation by the European Medicines Agency which may approve it later in 2019. It is approved for use by the United States Food and Drug Administration, but it is not yet widely available. Other drugs (such as 4-factor prothrombin complex concentrate) may be used but have limited data.

Dabigatran (FAQ5c)

Descriptive Evidence Summary

Yes. Idarucizumab is a specific reversal agent, approved by the European Medicines Agency and the United States Food and Drug Administration under the brand name Praxbind. Other drugs (such as 4-factor prothrombin complex concentrate) may be used but have limited data.

Edoxaban (FAQ5d)

Descriptive Evidence Summary

Not yet but this may change with new drugs. Andexanet alfa is a reversal agent that is undergoing evaluation by the European Medicines Agency which may approve it later in 2019. It is *not* approved for use by the United States Food and Drug Administration despite edoxaban being a factor Xa inhibitor, but it is suggested by some for off-label use. It is not yet widely available. Other drugs (such as 4-factor prothrombin complex concentrate) may be used but have limited data.

Rivaroxaban (FAQ5e)

Descriptive Evidence Summary

Not yet but this may change with new drugs. Andexanet alfa is a reversal agent that is undergoing evaluation by the European Medicines Agency which may approve it later in 2019. It is approved for use by the United States Food and Drug Administration, but it is not yet widely available. Other drugs (such as 4-factor prothrombin complex concentrate) may be used but have limited data.

FAQ 6: What do I do if I need surgery or a procedure?

Pre-Synthesis Efforts: Not applicable (descriptive summary provided)

For any patient, the specific decisions whether to interrupt anticoagulation, when to interrupt it, whether to provide bridge therapy, and when to restart the anticoagulant are based on clinical judgment considering many factors, including the risk of bleeding related to the procedure, the risk of bleeding related to patient factors, the risk of thromboembolism related to the procedure, the risk of thromboembolism related to patient factors (including thromboembolism for reasons other than atrial fibrillation), and the conditions and medications affecting drug metabolism and clearance. The answers here represent common patterns and do not substitute for individualized clinical decision-making. Additional details from Doherty 2017 are provided in Part 4.

Vitamin K antagonists (FAQ6a)

Descriptive Evidence Summary

It depends on the type of surgery, the patient's risk of bleeding and risk of thromboembolism, and the patient's INR (International Normalized Ratio of prothrombin time) values 5 to 7 days before the surgery. A common approach is to stop the anticoagulant 5 days before surgery, and to restart it within 24 hours after surgery. If the risk of blood clots is high an anticoagulant by injection may be given while off the oral drug.

Apixaban (FAQ6b)

Descriptive Evidence Summary

It depends on the type of surgery, the patient's risk of bleeding and risk of thromboembolism, and kidney function. A common approach is to stop apixaban at least 1 to 2 days before surgery, and to restart it 1 to 2 days after surgery.

Dabigatran (FAQ6c)

Descriptive Evidence Summary

It depends on the type of surgery, the patient's risk of bleeding and risk of thromboembolism, and kidney function. A common approach is to stop dabigatran at least 1 to 2 days before surgery, and to restart it 1 to 2 days after surgery.

Edoxaban (FAQ6d)

Descriptive Evidence Summary

It depends on the type of surgery, the patient's risk of bleeding and risk of thromboembolism, and kidney function. A common approach is to stop edoxaban at least 1 to 2 days before surgery, and to restart it 1 to 2 days after surgery.

Rivaroxaban (FAQ6e)

Descriptive Evidence Summary

It depends on the type of surgery, the patient's risk of bleeding and risk of thromboembolism, and kidney function. A common approach is to stop rivaroxaban at least 1 to 2 days before surgery, and to restart it 1 to 2 days after surgery.

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