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**OREGON HEALTH AND SCIENCE UNIVERSITY**
**OFFICE OF CLINICAL INTEGRATION AND EVIDENCE-BASED PRACTICE**

# Evidence-Based Practice Summary
# Rivaroxaban and Apixaban for DVT/VTE Prophylaxis

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## BACKGROUND

Total hip (THA) and total knee arthroplasty (TKA) are two of the most commonly performed operations in orthopedic surgery. The most common serious complication after THA and TKA is venous thromboembolism (VTE). Without efficacious anticoagulant prophylaxis, symptomatic deep venous thrombosis (DVT) may occur in 15%–30% and fatal pulmonary embolism may occur in 0.5%–2% of the patients undergoing THAs or TKAs. With modern surgical techniques and methods of preventing VTE including earlier mobilization and chemoprophylaxis, the rate of VTE has decreased over time. Currently in the United States, any VTE after THA and TKA is considered a preventable complication. Developing a VTE prophylaxis regimen with optimal efficacy and safety profiles is essential. However, the use of potent anticoagulation has been associated with higher rates of complications, such a bleeding. The most commonly used chemoprophylaxis after THAs and TKAs include low-molecular-weight heparin (LMWH), adjusted-dose warfarin, enoxaparin, and aspirin. However, due to the limitations of these drugs, new oral anticoagulants have been developed. Rivaroxaban and apixaban are both direct factor Xa (FXa) inhibitors. Rivaroxaban and Apixaban are currently approved in the United States for VTE prophylaxis after THAs and TKAs (Russell 2012).

## ASK THE QUESTION

**Question 1**: In patients who have undergone total hip arthroplasty (THA) or total knee arthroplasty (TKA) does a prophylactic oral anti-coagulant (rivaroxaban and apixaban) post-operatively prevent deep vein thrombosis (DVT)/ pulmonary embolism (PE)?

## SEARCH FOR EVIDENCE

**Databases** included Ovid MEDLINE, Cochrane Database of Systematic Reviews, PsycINFO, and National Guideline Clearinghouse, also looked at references and citing articles

**Search strategy** included:

1 exp arthroplasty, replacement, hip/ or exp hip prosthesis/ or exp arthroplasty, replacement, knee/ or exp knee prosthesis/ (53884)
2 exp Anticoagulants/ad, ae, ct, tu, to [Administration & Dosage, Adverse Effects, Contraindications, Therapeutic Use, Toxicity] (88894)
3 exp Blood Coagulation Factors/ai (14279)
4 2 or 3 (101886)
5 exp Thrombosis/pc [Prevention & Control] (17816)
6 exp Pulmonary Embolism/pc [Prevention & Control] (4687)
7 exp "embolism and thrombosis"/ (203421)
8 exp Preventive Health Services/ (519938)
9 7 and 8 (2306)
10 5 or 6 or 9 (22223)
11 1 and 4 and 10 (787)
12 ((rivaroxaban or aspirin or lovenox or warfarin or anti-coag* or anticoag* or ((factor or coagulat*) adj2 (inhibit* or block or antagon*))) adj10 (prevent* or prophyla*) adj5 (embol* or thrombo* or clot or clots)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3926)
13 1 and 12 (269)
14 ((thromboprophyl* or ((prevent* or prophyla*) adj5 (embol* or thrombo* or clot or clots))) adj10 ((hip or hips or knee* or joint* or arthroplas*) adj3 replac*)).mp. (610)
15 4 and 14 (484)
16 ((rivaroxaban or aspirin or lovenox or warfarin or anti-coag* or anticoag* or ((factor or coagulat*) adj2 (inhibit* or block or antagon*))) adj10 ((hip or hips or knee* or joint* or arthroplas*) adj3 replac*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1093)
17 10 and 16 (537)

18 12 and 14 and 16 (100)
19 11 or 13 or 15 or 17 or 18 (1219)
20 remove duplicates from 19 (1194)
21 limit 20 to english language (1066)
22 limit 20 to abstracts (988)
23 21 or 22 (1164)
24 limit 23 to (comparative study or controlled clinical trial or guideline or meta analysis or randomized controlled trial or systematic reviews) (504)
25 exp Epidemiologic Studies/ (2091730)
26 23 and 25 (346)
27 24 or 26 (664)
28 23 not 27 (500)

**Filters/limits** included systematic reviews published in English in the last 3 years.

## CRITICALLY ANALYZE THE EVIDENCE

The literature search resulted in more than 600 articles that analyzed oral anticoagulants (DOACs) after THA and TKA. We narrowed the search to include systematic reviews and relevant observational studies from 2013-2017. We identified nine studies that analyzed the effects of prophylactic DOACs in the prevention of VTE/DVT and included the outcome of major bleeding. In order to simplify the review process, we grouped the evidence into DOAC with outcomes: (1) VTE/DVT Prophylaxis with Rivaroxaban; (2) Major Bleeding with Rivaroxaban Use; (3) VTE/DVT Prophylaxis with Apixaban; (4) Major Bleeding with Apixaban Use; (5) Pooled Studies that included Rivaroxaban and/or Apixaban for DVT/VTE Prophylaxis, and (6) Pooled Studies of Major Bleeding with Rivaroxaban and/or Apixaban use:

1. VTE/DVT Prophylaxis with Rivaroxaban: Five studies, including four systematic reviews and one observational study, examined rivaroxaban use for VTE/DVT prophylaxis. One study compared rivaroxaban with apixaban and found that rivaroxaban use was associated with 4 fewer VTEs than apixaban (95% CI 9 fewer to 1 more) per 1000 patients (RR, 0.59 [95% CI 0.26-1.33]) (Adam 2013). Feng (2015) conducted a systematic review to analyze the efficacy of factor Xa inhibitors for thomboprophylaxis and demonstrated a lower occurrence of total VTE when the intervention drug was rivaroxaban (RR 0.70, 95%CI 0.60 to 0.81). An observational study observed the circulating concentrations of rivaroxaban and apixaban in patients to improve the knowledge of coagulation with these drugs (Freyburger 2015). The samples from T1 to T4 exhibiting rivaroxaban plasma concentrations higher

than 100ng/ml testified to a mean antithrombin increase of 24% when compared to the pretreatment T0 samples (P=0.007), whereas the 39 samples exhibiting apixaban plasma concentrations higher than 100ng/ml demonstrated a mean antithrombin increase of 18% (P=0.007 and 0.0002, respectively). Hamidi (2013) conducted a systematic review to assess the efficacy of rivaroxaban relative to enoxaparin. There was a statistically significant decrease in DVTs compared to enoxaparin in THA and TKAs (RR 0.21 [95%CI 0.14-0.32] and RR 0.62 [95%CI 0.51-0.75], respectively). Ma (2015) also conducted a systematic review to compare rivaroxaban with enoxaparin in total knee replacements. Their findings were similar and found a statistically significant decrease in DVTs with rivaroxaban use (RR = 0.59 [95% CI: 0.48-0.72, P< 0.01]).

*Overall Level of Evidence: Moderate*

2. Major Bleeding with Rivaroxaban Use: Five studies, including four systematic reviews and one retrospective cohort study, examined the risk of major bleeding with rivaroxaban use for VTE/DVT prophylaxis. The first systematic review (Adam 2013) compared the risk and benefits of DOACs versus standard prophylaxis. Their review found that rivaroxaban resulted in more clinically relevant bleeding events than apixaban (RR, 1.52 [CI, 1.19 to 1.95]), and the risk for major bleeding was also increased with rivaroxaban compared with apixaban (RR, 1.59 [CI, 0.84 to 3.02]). Feng (2015) conducted a systematic review to analyze the efficacy of factor Xa inhibitors for thomboprophylaxis and found a higher occurrence of bleeding complications when the intervention drug was rivaroxaban (RR 1.52, 1.14 to 2.02, P=0.004; Q=34.80, P=0.041; I2=36.8%). When reviewing the relationship between rivaroxaban dosing and a complication rate they found for rivaroxaban, there was a linear relationship between the treatment dose of rivaroxaban and the bleeding complication rate (RR:1.031, 1.018 to 1.044, P = 0.000). Higher rivaroxaban doses were associated with more major bleeding or clinically relevant non-major bleeding. A 5 mg increase of treatment dose was associated with a 13% increase of bleeding risk (RR: 1.168, 1.098 to 1.243, P =0.000). Hamidi (2013) conducted a systematic review to assess the efficacy of rivaroxaban relative to enoxaparin. There was a statistically significant increased risk of major bleeding with rivaroxaban compared to enoxaparin in THAs and TKAs (RR 2.23 [95%CI 1.06-4.67] and RR 1.61 [95%CI 0.80-3.24], respectively). A retrospective cohort study (Ricket 2016) evaluated the bleeding events between patients who received enoxaparin or rivaroxaban for prevention of venous thromboembolism (VTE) following total hip arthroplasty (THA) or total knee arthroplasty (TKA). Postoperative bleeding, defined in this study as a composite of major bleeding and clinically relevant non-major bleeding, was lower in the enoxaparin group compared to the rivaroxaban group (2.2% vs 6.3%, P < 0.01). In another systematic review, Russell et al (2013) analyzed the data from the new oral direct Factor Xa inhibitors including rivaroxaban for VTE and DVT prophylaxis. They found a trend for an increased risk of major bleeding in patients taking rivaroxaban (OR 1.81, 95% CI 0.91–3.62, p =0.09).

*Overall Level of Evidence: Moderate*

3. VTE/DVT Prophylaxis with Apixaban: Four studies, including three systematic reviews and one observational study, examined apixaban use for VTE/DVT prophylaxis.The first systematic review (Adam 2013) compared rivaroxaban with apixaban and found that rivaroxaban was associated with 4 fewer VTEs than apixaban (95% CI 9 fewer to 1 more) per 1000 patients (RR, 0.59 [95% CI 0.26-1.33]). Feng (2015) conducted a systematic review to analyze the efficacy of factor Xa inhibitors for thomboprophylaxis and demonstrated a lower occurrence of total VTE when the intervention drug was apixaban (RR 0.62, 0.47 to 0.81, P=0.001) compared to enoxaparin. An observational study observed the circulating concentrations of rivaroxaban and apixaban in patients to improve the knowledge of coagulation with these drugs (Freyburger 2015). The samples from T1 to T4 exhibiting rivaroxaban plasma concentrations higher than 100 ng/ml testified to a mean antithrombin increase of 24% when compared to the pretreatment T0 samples (P=0.007), whereas the 39 samples exhibiting apixaban plasma concentrations higher than 100 ng/ml demonstrated a mean antithrombin increase of 18% (P=0.007 and 0.0002, respectively). Ma (2015) also conducted a systematic review to compare apixaban with enoxaparin in total knee replacements. The subgroup analysis of apixaban studies found that apixaban lowered the risk of DVTs compared to enoxaparin (RR = 0.68, 95% CI: 0.59-0.79, P < 0.01). However, further analysis stratified by the regimen of enoxaparin did not find a significant difference between apixaban and 30 mg b.i.d dose of enoxaparin (RR = 0.85, 95% CI: 0.66-1.10, P < 0.01).

*Overall Level of Evidence: Moderate*

4. Major Bleeding with Apixaban Use: Two systematic reviews examined the risk of major bleeding with apixaban use for VTE/DVT prophylaxis.Feng (2015) conducted a systematic review to analyze the efficacy of factor Xa inhibitors for thomboprophylaxis and did not find a higher occurrence of bleeding complications when the intervention drug was apixaban (RR 0.88, 0.73 to 1.06). For apixaban, major bleeding did not show linear relationship with the treatment dose (RR: 1.027, 0.968 to 1.090) nor a nonlinear relationship (RR at 50% percentile: 1.032, 0.871 to 1.223). In another systematic review, Russell et al (2013) analyzed the data from the new oral direct Factor Xa inhibitors including rivaroxaban for VTE and DVT prophylaxis. There was a trend for an increased risk of major bleeding in patients taking rivaroxaban (OR 1.81, 95% CI 0.91–3.62, p =0.09), but not with apixaban (p = 0.33). There was no difference between the oral FXa inhibitors and enoxaparinin the rates of major plus clinically relevant non-major bleeding (p = 0.91). However, there was a trend toward fewer events in the patients taking apixaban (OR 0.8, 95% CI 0.64–1.01, p = 0.06).

*Overall Level of Evidence: Moderate*

5. Pooled Studies that included Rivaroxaban and/or Apixaban for DVT/VTE Prophylaxis: Three systematic reviews combined the results of multiple DOACs to assess their effectiveness for VTE/DVT prophylaxis. One systematic review (Forster 2016) assessed the effects of extended-duration anticoagulant thromboprophylaxis for the prevention of VTE in people undergoing elective THA or TKA by pooling multiple studies that investigated various Direct Oral Anticoagulants (DOACs). For symptomatic VTEs compared to placebo, DOACs decreased odds of a symptomatic VTE (OR 0.20 [95% CI 0.06-0.68]). DOACs did not

significantly decrease the odds of symptomatic VTEs compared to heparin (OR 0.70 [95% CI 0.28-1.70]). Another systematic review (Russell 2013) analyzed the data from the new oral direct Factor Xa inhibitors for VTE and DVT prophylaxis. The pooled analysis revealed that Factor Xa inhibitors decreased the odds for total VTE and death as well as DVT (OR 0.38 [95%CI 0.23–0.61] p < 0.0001 and OR 0.36 [95% CI 0.2–0.62] p= 0.0003, respectively). The third systematic (Squizzato 2015) review sought to determine the incidence of post-operative arterial thrombosis is patients treated with DOACs and heparin undergoing TKA and THA. The combined data from THR and TKR studies, showed that DOACs and enoxaparin were associated with similar risks for both total arterial thrombosis (OR 0.86 [95 %CI, 0.53-1.40] $I^2$=11), and major vascular events (OR 0.97 [95 %CI, 0.69-1.36] $I^2$=0).

6. Pooled Studies of Major Bleeding with Rivaroxaban and/or Apixaban use: Three systematic reviews combined the results of multiple DOACs to assess their risk of major bleeding. One systematic review (Forster 2016) assessed the effects of extended-duration anticoagulant thromboprophylaxis for the prevention of VTE in people undergoing elective THA or TKA by pooling multiple studies that investigated various DOACs. There were no major differences in major bleeding between DOACs and placebo (OR 1.00 [95% CI 0.06-16.02]) or clinically relevant bleeding (OR 1.22 [95% CI 0.76-1.95]). Ma (2015) also conducted a systematic review to compare rivaroxaban with enoxaparin in total knee replacements. The pooled analysis revealed no major difference between rivaroxaban/apixaban and enoxaparin in terms of risk of major bleeding (RR 0.72 [95% CI: 0.44-1.17]). A third systematic review (Squizzato 2015) sought to determine the incidence of post-operative arterial thrombosis is patients treated with DOAC and heparin undergoing TKA and THA. DOACs and enoxaparin were similar at the fixed-effect model in the risk of major bleeding plus clinically relevant bleeding (OR 1.03; 95 %CI, 0.92, 1.15; $I^2$=38).

**Conclusion:** Overall, there is moderate quality evidence to show that prophylactic use of both apixaban and rivaroxaban decreases the risk of DVT after a TKA or THA. There is moderate quality evidence that suggests a minor increased risk of major bleeding with the use of rivaroxaban, but not with apixaban.

| **PICO Question: In patients who have undergone total hip arthroplasty (THA) or total knee arthroplasty (TKA) does a prophylactic direct oral anticoagulant (rivaroxaban and apixaban) post-operatively) prevent deep vein thrombosis (DVT)/ pulmonary embolism (PE)?** | | | | | | Lower Quality Rating if:<br>☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*<br><br>☐ Studies are indirect *(PICO question is quite different from the* |
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| **Outcome: VTE/ DVT Prophylaxis**<br>**Modality: Rivaroxaban** | | | | | | |
| *Author/Date* | *Purpose of Study* | *Study Design & Methods* | *Sample* | *Outcomes* | *Design Limitations* | |
| **Total # of Studies: 8 # of Systematic Reviews: 7 # of Non-Randomized Studies: 1** | | | | | | |
| Adam, S. S., et al. (2013). *Annals of* | To compare the benefits and risks of | Systematic review with meta-analysis | 16 studies, 38, 747 participants | Rivaroxaban vs dabigatran<br>RR, 0.68 (95% CI 0.21-2.23)<br>RD, 3 fewer ( 11 fewer to 4 more) events | Study Limitations =<br>☐ None<br>***Systematic Review***<br>☐ Review did not address | |

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| *Internal Medicine* | new oral anticoagulants (NOACs) vs standard thromboproph ylaxis. | | | per 1000 pts<br><br>**Rivaroxaban vs apixaban**<br>**RR, 0.59 (95% CI 0.26-1.33)**<br>**RD, 4 fewer ( 9 fewer to 1 more)per 1000 pts** | focused clinical question<br>☐ Search was not detailed or exhaustive<br>☐ Quality of the studies was not appraised or studies were of low quality<br>☒ Methods and/or results were inconsistent across studies | *available evidence in regard to population, intervention, comparison, or outcome)*<br><br>☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*<br><br>☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*<br><br><u>Increase Quality Rating if:</u><br>☐ Large Effect<br>☐ Dose-response gradient<br>☐ Plausible confounders or other biases increase certainty of effect<br><br>Quality (certainty) of evidence for studies as a whole:<br>☐ High<br>☒ Moderate<br>☐ Low<br>☐ Very Low |
| Feng, W., et al. (2015). *Thrombosis Research* | To analyze the efficacy and safety of direct factor Xa inhibitors for thromboproph ylaxis after total hip or knee replacement. To delineate the dose response effect of direct factor Xa inhibitors. To compare the efficacy between any two direct factor Xa inhibitors. | Systemic review, traditional meta-analysis, dose-response meta-analysis and network meta-analysis | 7 studies, 5429 participants | Lower occurrence of total VTE was shown when the intervention drug was rivaroxaban (RR 0.70, 0.60 to 0.81, P=0.000; P=0.035; I2=37.4%) | Study Limitations =<br>☒ None<br>***Systematic Review***<br>☐ Review did not address focused clinical question<br>☐ Search was not detailed or exhaustive<br>☐ Quality of the studies was not appraised or studies were of low quality<br>☐ Methods and/or results were inconsistent across studies | |
| Forster, R. and M. Stewart (2016). *Cochrane Database of Systematic Reviews* | To assess the effects of extended-duration anticoagulant thromboproph ylaxis for the prevention of venous thromboembo | Systematic review with meta-analysis | 4 studies, 9639 participants (DOACs investigated included rivaroxaban) | **DOAC vs placebo**:<br>Symptomatic VTE: OR 0.20 (95% CI 0.06-0.68)<br><br>**DOAC vs heparin:**<br>Symptomatic VTE: OR 0.70 (95%CI 0.28-1.70) | Study Limitations =<br>☐ None<br>***Systematic Review***<br>☐ Review did not address focused clinical question<br>☐ Search was not detailed or exhaustive<br>☐ Quality of the studies was not appraised or studies were of low quality<br>☒ Methods and/or results were inconsistent across studies | |

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| | lism (VTE) in people undergoing elective hip or knee replacement surgery or hip fracture repair. | | | | | |
| Freyburger, G., et al. (2015). Blood *Coagulation & Fibrinolysis* | The aim of this study was to improve knowledge of what happens in the coagulation of orthopaedic patients under rivaroxaban and apixaban, in order to finalize and cross-validate effective measurement methods and to provide arguments for helping to reference one or the other drug. | observational, nonrandomized, one-period comparison study on behalf of the Committee for Health Products and Therapeutic Innovation of the University Hospital of Bordeaux | 102 patients ( 51 received rivaroxaban and 51 received apixaban) | After 1 week of treatment, the drugs differed: Cmax and Ctrough were closer when apixaban was taken twice daily (83±39 and 58±17ng/ml) than with rivaroxaban taken once a day (113±67 and 13±20ng/ml).<br><br>The 53 samples from T1 to T4 exhibiting rivaroxaban plasma concentrations higher than 100ng/ml testify to a mean antithrombin increase of 24% when compared to the 51 pretreatment T0 samples (P=0.007), whereas the 39 samples exhibiting apixaban plasma concentrations higher than 100ng/ml demonstrate a mean antithrombin increase of 18% (P=0.007 and 0.0002, respectively)<br><br>Although rivaroxaban and apixaban present apparently similar constant rates, they exhibit significant differences in their concentrations and anticoagulant effects when studied ex vivo in orthopedic patients. | Study Limitations =<br>☐ None<br>***Non-Randomized Studies***<br>☐ Failure to develop and apply appropriate eligibility criteria<br>☐ Flawed measurement of both exposure and outcome<br>☒ Failure to adequately control confounding<br>☐ Incomplete or inadequately short follow-up<br>☐ Differences in important prognostic factors at baseline | |
| Hamidi, V., et al. (2013). *International Journal of Technology Assessment in Health Care* | To assess the relative efficacy and cost-effectiveness of two new oral anticoagulants , rivaroxaban and dabigatran, relative to subcutaneous enoxaparin | Systematic Review with meta-analysis | 5 studies, 8878 participants | **DVT-Total Hip replacement:**<br>RR 0.21 (95%CI 0.14-0.32)<br><br>**DVT-Total knee replacement**:<br>RR 0.62 (95%CI 0.51-0.75) | Study Limitations =<br>☒ None<br>***Systematic Review***<br>☐ Review did not address focused clinical question<br>☐ Search was not detailed or exhaustive<br>☐ Quality of the studies was not appraised or studies were of low quality<br>☐ Methods and/or results were inconsistent across studies | |

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| | for the prevention of thromboembolism after total hip replacement (THR) and total knee replacement surgery (TKR) | | | | | |
| Ma, G., et al. (2015). *Thrombosis Research* | To compare the efficacy and safety of direct factor Xa inhibitors (rivaroxaban and apixaban) with enoxaparin for the prevention of venous thromboembolism (VTE) after total knee replacement. | Systematic Review | 2 studies, 5679 participants | DVT:<br>RR = 0.59 (95% CI: 0.48-0.72, P< 0.01; P heterogeneity = 0.17, I2=47%) | Study Limitations =<br>☒ None<br>***Systematic Review***<br>☐ Review did not address focused clinical question<br>☐ Search was not detailed or exhaustive<br>☐ Quality of the studies was not appraised or studies were of low quality<br>☐ Methods and/or results were inconsistent across studies | |
| Russell, R. D. and M. H. Huo (2013). *Journal of Arthroplasty* | To analyze data from all of the phase III clinical trials for both newer oral direct FXa inhibitors for VTE prophylaxis in patients undergoing THAs and TKAs | Systematic Review | 4 studies, 12,726 patients | **VTE + death**<br>OR 0.38 ( 95%CI 0.23–0.61) p < 0.0001<br>**DVT**<br>OR 0.36 ( 95% CI 0.2–0.62) p= 0.0003 | Study Limitations =<br>☐ None<br>***Systematic Review***<br>☐ Review did not address focused clinical question<br>☐ Search was not detailed or exhaustive<br>☐ Quality of the studies was not appraised or studies were of low quality<br>☒ Methods and/or results were inconsistent across studies | |
| Squizzato, A., et al. (2015). *Thrombosis & Haemostasis* | the aim of determining: 1) the incidence of postoperative arterial thrombosis | Systematic Review | 4 studies, 12,726 patients | THR<br>NOACs and enoxaparin were similar at the fixed-effect model in the risk of pulmonary embolism (OR 0.94; 95 %CI, 0.47,1.85; $I^2$=23), major vascular events (OR 0.97; 95 %CI, 0.61,1.55; $I^2$=0) | Study Limitations =<br>☐ None<br>***Systematic Review***<br>☐ Review did not address focused clinical question<br>☐ Search was not detailed or exhaustive | |

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| | (AT) in NOACs-treated and LMWH-treated patients undergoing elective TKR or THR during active treatment and during follow-up;2) the incidence of patient-relevant outcomes (i. e. prevention of major symptomatic thrombotic events and/or total mortality with minimal risk of major bleeding) with NOACs compared with standard therapy. | | | TKR arterial thrombosis:<br>NOACs and enoxaparin were similar at the fixed-effect model in the risk of pulmonary embolism (OR 1.27; 95 %CI, 0.76, 2.11; $I^2$=40), major vascular events (OR 1.06; 95 %CI, 0.66, 1.71; $I^2$=51),<br><br>The combined data from THR and TKR studies, NOACs and enoxaparin were similar at fixed-effect model in the risk of major efficacy and safety outcomes, in particular in the risk of total arterial thrombosis (OR 0.86; 95 %CI, 0.53, 1.40; $I^2$=11), major vascular events (OR 0.97; 95 %CI, 0.69, 1.36; $I^2$=0) | ☐ Quality of the studies was not appraised or studies were of low quality<br>☒ Methods and/or results were inconsistent across studies | |

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

| **PICO Question: In patients who have undergone total hip arthroplasty (THA) or total knee arthroplasty (TKA) does a prophylactic direct oral anticoagulant (rivaroxaban and apixaban) post-operatively) prevent deep vein thrombosis (DVT)/ pulmonary embolism (PE)?**<br>**Outcome: Major Bleeding**<br>**Modality: Rivaroxaban** | | | | | | Lower Quality Rating if:<br>☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*<br><br>☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention,* |
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| *Author/Date* | *Purpose of Study* | *Study Design & Methods* | *Sample* | *Outcomes* | *Design Limitations* | |
| **Total # of Studies: 8 # of Systematic Reviews: 7 # of Non-Randomized Studies: 1** | | | | | | |
| Adam, S. S., et al. (2013). *Annals of* | To compare the benefits and risks of | Systematic review with meta-analysis | 16 studies, 38, 747 participants | Rivaroxaban resulted in more clinically relevant bleeding events than apixaban (RR, 1.52 [CI, 1.19 co 1.95]). | Study Limitations =<br>☐ None<br>***Systematic Review***<br>☐ Review did not address | |

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| *Internal Medicine* | new oral anticoagulants (NOACs) vs standard thromboproph ylaxis. | | | Risk for major bleeding was also increased with rivaroxaban compared with apixaban (RR, 1.59 [CI, 0.84 to 3.02]) | focused clinical question<br>☐ Search was not detailed or exhaustive<br>☐ Quality of the studies was not appraised or studies were of low quality<br>☒ Methods and/or results were inconsistent across studies | *comparison, or outcome)*<br><br>☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*<br><br>☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*<br><br><u>Increase Quality Rating if:</u><br>☐ Large Effect<br>☐ Dose-response gradient<br>☐ Plausible confounders or other biases increase certainty of effect<br><br>Quality (certainty) of evidence for studies as a whole:<br>☐ High<br>☒ Moderate<br>☐ Low<br>☐ Very Low |
| Feng, W., et al. (2015). *Thrombosis Research* | To analyze the efficacy and safety of direct factor Xa inhibitors for thromboproph ylaxis after total hip or knee replacement. To delineate the dose response effect of direct factor Xa inhibitors. To compare the efficacy between any two direct factor Xa inhibitors. | Systemic review, traditional meta-analysis, dose-response meta-analysis and network meta-analysis | 7 studies, 5429 participants | Higher occurrence of bleeding complication was shown when the intervention drug was rivaroxaban (RR 1.52, 1.14 to 2.02, P = 0.004; Q=34.80, P=0.041; $I_2$=36.8%)<br><br>For rivaroxaban, there was a linear relationship between the treatment dose of rivaroxaban and the bleeding complication rate (RR: 1.031, 1.018 to 1.044, P = 0.000). Higher rivaroxaban doses were associated with more major bleeding or clinically relevant but non-major bleeding. A 5 mg increase of treatment dose was associated with a 13% increase of bleeding risk (RR: 1.168, 1.098 to 1.243, P = 0.000). | Study Limitations =<br>☒ None<br>***Systematic Review***<br>☐ Review did not address focused clinical question<br>☐ Search was not detailed or exhaustive<br>☐ Quality of the studies was not appraised or studies were of low quality<br>☐ Methods and/or results were inconsistent across studies | |
| Forster, R. and M. Stewart (2016). *Cochrane Database of Systematic Reviews* | To assess the effects of extended-duration anticoagulant thromboproph ylaxis for the prevention of venous thromboembo | Systematic review with meta-analysis | 4 studies, 9639 participants (DOACs investigated included rivaroxaban) | **DOAC vs placebo**:<br>Major Bleeding: OR 1.00 (95% CI 0.06-16.02)<br>Clinically relevant bleeding: OR 1.22 (95% CI 0.76-1.95) | Study Limitations =<br>☐ None<br>***Systematic Review***<br>☐ Review did not address focused clinical question<br>☐ Search was not detailed or exhaustive<br>☐ Quality of the studies was not appraised or studies were of low quality<br>☒ Methods and/or results | |

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| | lism (VTE) in people undergoing elective hip or knee replacement surgery or hip fracture repair. | | | | were inconsistent across studies | |
| Hamidi, V., et al. (2013). *International Journal of Technology Assessment in Health Care* | To assess the relative efficacy and cost-effectiveness of two new oral anticoagulants , rivaroxaban and dabigatran, relative to subcutaneous enoxaparin for the prevention of thromboembolism after total hip replacement (THR) and total knee replacement surgery (TKR) | Systematic Review with meta-analysis | 5 studies, 8878 participants | **Major Bleeding-Total Hip replacement:** RR 2.23 (95%CI 1.06-4.67)<br><br>**Major Bleeding-Total knee replacement**: RR 1.61 (95%CI 0.80-3.24) | Study Limitations =<br>☒ None<br>***Systematic Review***<br>☐ Review did not address focused clinical question<br>☐ Search was not detailed or exhaustive<br>☐ Quality of the studies was not appraised or studies were of low quality<br>☐ Methods and/or results were inconsistent across studies | |
| Ma, G., et al. (2015). *Thrombosis Research* | To compare the efficacy and safety of direct factor Xa inhibitors (rivaroxaban and apixaban) with enoxaparin for the prevention of venous | Systematic Review | 2 studies, 5679 participants | Major Bleeding:<br>Pooled RR( rivaroxaban/ apixaban) = 0.72 (95% CI: 0.44-1.17, | Study Limitations =<br>☐ None<br>***Systematic Review***<br>☐ Review did not address focused clinical question<br>☐ Search was not detailed or exhaustive<br>☐ Quality of the studies was not appraised or studies were of low quality<br>☒ Methods and/or results were inconsistent across studies | |

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| | thromboembolism (VTE) after total knee replacement. | | | | | |
| Ricket, A. L., et al. (2016). *Annals of Pharmacotherapy* | To evaluate bleeding events between patients who received enoxaparin or rivaroxaban for prevention of venous thromboembolism (VTE) following total hip arthroplasty (THA) or total knee arthroplasty (TKA). | Retrospective cohort study | 3 cohorts, 878 participants | Major bleeding<br>Any postoperative bleeding, defined in this study as a composite of major bleeding and clinically relevant non-major bleeding, was lower in the enoxaparin group compared to the rivaroxaban group (2.2% vs 6.3%, P < 0.01). | Study Limitations =<br>☐ None<br>***Non-Randomized Studies***<br>☐ Failure to develop and apply appropriate eligibility criteria<br>☐ Flawed measurement of both exposure and outcome<br>☐ Failure to adequately control confounding<br>☐ Incomplete or inadequately short follow-up<br>☒ Differences in important prognostic factors at baseline | |
| Russell, R. D. and M. H. Huo (2013). *Journal of Arthroplasty* | To analyze data from all of the phase III clinical trials for both newer oral direct FXa inhibitors for VTE prophylaxis in patients undergoing THAs and TKAs | Systematic Review | 4 studies, 12,726 patients | There was a trend for an increased risk of major bleeding<br>in patients taking rivaroxaban (OR 1.81, 95% CI 0.91–3.62, p =0.09) | Study Limitations =<br>☐ None<br>***Systematic Review***<br>☐ Review did not address focused clinical question<br>☐ Search was not detailed or exhaustive<br>☐ Quality of the studies was not appraised or studies were of low quality<br>☒ Methods and/or results were inconsistent across studies | |
| Squizzato, A., et al. (2015). *Thrombosis & Haemostasis* | the aim of determining: 1) the incidence of postoperative arterial thrombosis (AT) in NOACs-treated and LMWH-treated | Systematic Review | 4 studies, 12,726 patients | NOACs and enoxaparin were similar at the fixed-effect model in<br>the risk of major bleeding + clinically relevant bleeding (OR 1.03; 95 %CI, 0.92, 1.15; $I^2$=38) | Study Limitations =<br>☐ None<br>***Systematic Review***<br>☐ Review did not address focused clinical question<br>☐ Search was not detailed or exhaustive<br>☐ Quality of the studies was not appraised or studies were of low quality<br>☒ Methods and/or results were inconsistent across | |

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| | patients undergoing elective TKR or THR during active treatment and during follow-up;2) the incidence of patient-relevant outcomes (i. e. prevention of major symptomatic thrombotic events and/or total mortality with minimal risk of major bleeding) with NOACs compared with standard therapy. | | | | studies | |

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

| **PICO Question: In patients who have undergone total hip arthroplasty (THA) or total knee arthroplasty (TKA) does a prophylactic direct oral anticoagulant (rivaroxaban and apixaban) post-operatively) prevent deep vein thrombosis (DVT)/ pulmonary embolism (PE)?** | | | | | | Lower Quality Rating if: ☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)* ☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention,* |
|---|---|---|---|---|---|---|
| **Outcome: VTE/ DVT Prophylaxis**<br>**Modality: Apixaban** | | | | | | |
| *Author/Date* | *Purpose of Study* | *Study Design & Methods* | *Sample* | *Outcomes* | *Design Limitations* | |
| **Total # of Studies: 7# of Systematic Reviews: 6 # of Non-Randomized Studies: 1** | | | | | | |
| Adam, S. S., et al. (2013). *Annals of Internal Medicine* | To compare the benefits and risks of new oral anticoagulants (NOACs) vs | Systematic review with meta-analysis | 16 studies, 38, 747 participants | **Rivaroxaban vs apixaban**<br>**RR, 0.59 (95% CI 0.26-1.33)**<br>**RD, 4 fewer ( 9 fewer to 1 more)per 1000 pts**<br><br>Apixaban vs. dabigatran<br>RR, 1.16 (0.31-4.28) | Study Limitations =<br>☐ None<br>***Systematic Review***<br>☐ Review did not address focused clinical question<br>☐ Search was not detailed or exhaustive | |

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| | standard thromboprophylaxis. | | | RD 1 more (7 fewer to 8 more) per 1000 pts | ☐ Quality of the studies was not appraised or studies were of low quality<br>☒ Methods and/or results were inconsistent across studies | *comparison, or outcome)*<br><br>☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*<br><br>☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*<br><br><u>Increase Quality Rating if:</u><br>☐ Large Effect<br>☐ Dose-response gradient<br>☐ Plausible confounders or other biases increase certainty of effect<br><br>Quality (certainty) of evidence for studies as a whole:<br>☐ High<br>☒ Moderate<br>☐ Low<br>☐ Very Low |
| Feng, W., et al. (2015). *Thrombosis Research* | To analyze the efficacy and safety of direct factor Xa inhibitors for thromboprophylaxis after total hip or knee replacement. To delineate the dose response effect of direct factor Xa inhibitors. To compare the efficacy between any two direct factor Xa inhibitors. | Systemic review, traditional meta-analysis, dose-response meta-analysis and network meta-analysis | 7 studies, 5429 participants | Lower occurrence of total VTE was shown when the intervention drug was apixaban (RR 0.62, 0.47 to 0.81, P=0.001; Q=20.88, P=0.007; I2=61.7%) compared to enoxaparin. | Study Limitations =<br>☒ None<br>***Systematic Review***<br>☐ Review did not address focused clinical question<br>☐ Search was not detailed or exhaustive<br>☐ Quality of the studies was not appraised or studies were of low quality<br>☐ Methods and/or results were inconsistent across studies | |
| Forster, R. and M. Stewart (2016). *Cochrane Database of Systematic Reviews* | To assess the effects of extended-duration anticoagulant thromboprophylaxis for the prevention of venous thromboembolism (VTE) in people undergoing elective hip or knee replacement | Systematic review with meta-analysis | 4 studies, 9639 participants (DOACs investigated included apixaban) | **DOAC vs heparin:**<br>Symptomatic VTE: OR 0.70 (95%CI 0.28-1.70) | Study Limitations =<br>☐ None<br>***Systematic Review***<br>☐ Review did not address focused clinical question<br>☐ Search was not detailed or exhaustive<br>☐ Quality of the studies was not appraised or studies were of low quality<br>☒ Methods and/or results were inconsistent across studies | |

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| | surgery or hip fracture repair. | | | | | |
| Freyburger, G., et al. (2015). Blood *Coagulation & Fibrinolysis* | The aim of this study was to improve knowledge of what happens in the coagulation of orthopaedic patients under rivaroxaban and apixaban, in order to finalize and cross-validate effective measurement methods and to provide arguments for helping to reference one or the other drug. | observational, nonrandomized, one-period comparison study on behalf of the Committee for Health Products and Therapeutic Innovation of the University Hospital of Bordeaux | 102 patients ( 51 received rivaroxaban and 51 received apixaban) | After 1 week of treatment, the drugs differed: Cmax and Ctrough were closer when apixaban was taken twice daily (83±39 and 58±17ng/ml) than with rivaroxaban taken once a day (113±67 and 13±20ng/ml).<br><br>The 53 samples from T1 to T4 exhibiting rivaroxaban plasma concentrations higher than 100ng/ml testify to a mean antithrombin increase of 24% when compared to the 51 pretreatment T0 samples (P=0.007), whereas the 39 samples exhibiting apixaban plasma concentrations higher than 100ng/ml demonstrate a mean antithrombin increase of 18% (P=0.007 and 0.0002, respectively)<br><br>Although rivaroxaban and apixaban present apparently similar constant rates, they exhibit significant differences in their concentrations and anticoagulant effects when studied ex vivo in orthopedic patients. | Study Limitations =<br>☐ None<br>***Non-Randomized Studies***<br>☐ Failure to develop and apply appropriate eligibility criteria<br>☐ Flawed measurement of both exposure and outcome<br>☒ Failure to adequately control confounding<br>☐ Incomplete or inadequately short follow-up<br>☐ Differences in important prognostic factors at baseline | |
| Ma, G., et al. (2015). *Thrombosis Research* | To compare the efficacy and safety of direct factor Xa inhibitors (rivaroxaban and apixaban) with enoxaparin for the prevention of venous thromboembolism (VTE) after total knee replacement. | Systematic Review | 3 studies, 6380 participants | DVT:<br>Subgroup analysis of apixaban studies (RR = 0.68, 95% CI: 0.59-0.79, P < 0.01; P heterogeneity = 0.01, I2 = 78%).<br><br>However, further analysis stratified by the regime of enoxaparin did not find a significant difference between apixaban and 30 mg b.i.d dose of enoxaparin (RR = 0.85, 95% CI: 0.66-1.10, P < 0.01; P heterogeneity = 0.03, I2 = 78%) | Study Limitations =<br>☒ None<br>***Systematic Review***<br>☐ Review did not address focused clinical question<br>☐ Search was not detailed or exhaustive<br>☐ Quality of the studies was not appraised or studies were of low quality<br>☐ Methods and/or results were inconsistent across studies | |
| Russell, R. D. and M. H. Huo (2013). *Journal of Arthroplasty* | To analyze data from all of the phase III clinical trials for both newer oral direct FXa | Systematic Review | 11,659 participants | **VTE + death**<br>Pooled data demonstrated that apixaban had a trend toward decreased events compared to enoxaparin (OR 0.59, 95% CI 0.34–1.02, p = 0.06) | Study Limitations =<br>☐ None<br>***Systematic Review***<br>☐ Review did not address focused clinical question<br>☐ Search was not detailed or | |

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| | inhibitors for VTE prophylaxis in patients undergoing THAs and TKAs | | | **DVT**<br>OR 0.55 (95% CI 0.32–0.95) p< 0.03 | exhaustive<br>☒ Quality of the studies was not appraised or studies were of low quality<br>☐ Methods and/or results were inconsistent across studies | |
| Squizzato, A., et al. (2015). *Thrombosis & Haemostasis* | the aim of determining: 1) the incidence of postoperative arterial thrombosis (AT) in NOACs-treated and LMWH-treated patients undergoing elective TKR or THR during active treatment and during follow-up;2) the incidence of patient-relevant outcomes (i. e. prevention of major symptomatic thrombotic events and/or total mortality with minimal risk of major bleeding) with NOACs compared with standard therapy. | Systematic Review | 3 studies, 2673 participants | TKR arterial thrombosis<br>OR 0.43 (95 %CI 0.08-2.37)<br><br>THR arterial thrombosis:<br>OR 1.66 (95 %CI 0.40- 6.95) | Study Limitations =<br>☐ None<br>***Systematic Review***<br>☐ Review did not address focused clinical question<br>☐ Search was not detailed or exhaustive<br>☐ Quality of the studies was not appraised or studies were of low quality<br>☒ Methods and/or results were inconsistent across studies | |

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

| **PICO Question: In patients who have undergone total hip arthroplasty (THA) or total knee arthroplasty (TKA) does a prophylactic direct** | Lower Quality Rating if: |
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| **oral anticoagulant (rivaroxaban and apixaban) post-operatively) prevent deep vein thrombosis (DVT)/ pulmonary embolism (PE)?** | | | | | | ☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*<br><br>☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*<br><br>☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)* |
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| **Outcome: Major Bleeding**<br>**Modality: Apixaban** | | | | | | |
| *Author/Date* | *Purpose of Study* | *Study Design & Methods* | *Sample* | *Outcomes* | *Design Limitations* | |
| **Total # of Studies: 6# of Systematic Reviews: 6** | | | | | | |
| Adam, S. S., et al. (2013). *Annals of Internal Medicine* | To compare the benefits and risks of new oral anticoagulants (NOACs) vs standard thromboprophylaxis. | Systematic review with meta-analysis | 16 studies, 38, 747 participants | The risk for major bleeding was lower with apixaban than with enoxaparin in TKR (RR 0.56, 95%CI 0.32-0.96) but not in THR (RR 1.22, 95%CI 0.65-2.26)<br><br>Risk for major bleeding was increased with rivaroxaban compared with apixaban (RR, 1.59 [CI, 0.84 to 3.02]) | Study Limitations =<br>☐ None<br>***Systematic Review***<br>☐ Review did not address focused clinical question<br>☐ Search was not detailed or exhaustive<br>☐ Quality of the studies was not appraised or studies were of low quality<br>☒ Methods and/or results were inconsistent across studies | |

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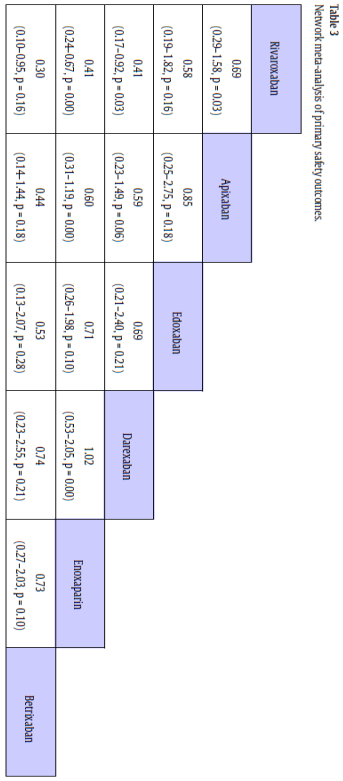
| Feng, W., et al. (2015). *Thrombosis Research* | To analyze the efficacy and safety of direct factor Xa inhibitors for thromboprophylaxis after total hip or knee replacement. To delineate the dose response effect of direct factor Xa inhibitors. To compare the efficacy between any two direct factor Xa inhibitors. | Systemic review, traditional meta-analysis, dose-response meta-analysis and network meta-analysis | 2 studies, 5052 participants | Table 3<br>Network meta-analysis of primary safety outcomes.<br>Ranking is given. Highest bleeding risk goes on the left to the lowest on the right.<br>  <br><br>For apixaban, its primary safety outcomes (major bleeding) did not show linear relationship with the treatment dose (RR: 1.027, 0.968 to 1.090, P = 0.371) nor non linear relationship as well (RR at 50% percentile: 1.032, 0.871 to 1.223, P = 0.708; RR at 95 percentile: 0.989, 0.729 to 1.342, P=0.948) | Study Limitations =<br>☒ None<br>***Systematic Review***<br>☐ Review did not address focused clinical question<br>☐ Search was not detailed or exhaustive<br>☐ Quality of the studies was not appraised or studies were of low quality<br>☐ Methods and/or results were inconsistent across studies | ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*<br><br>Increase Quality Rating if:<br>☐ Large Effect<br>☐ Dose-response gradient<br>☐ Plausible confounders or other biases increase certainty of effect<br><br>Quality (certainty) of evidence for studies as a whole:<br>☐ High<br>☒ Moderate<br>☐ Low<br>☐ Very Low |
| Forster, R. and M. Stewart (2016). *Cochrane Database of Systematic* | To assess the effects of extended-duration anticoagulant thromboprophyl | Systematic review with meta-analysis | 5 studies,16199 participants (DOACs investigated included apixaban) | **DOAC vs heparin:**<br>Bleeding events: OR 1.11 (95%CI 0.79-1.54) | Study Limitations =<br>☐ None<br>***Systematic Review***<br>☐ Review did not address focused clinical question<br>☐ Search was not detailed or exhaustive | |

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| *Reviews* | axis for the prevention of venous thromboembolism (VTE) in people undergoing elective hip or knee replacement surgery or hip fracture repair. | | | | ☐ Quality of the studies was not appraised or studies were of low quality<br>☒ Methods and/or results were inconsistent across studies | |
| Ma, G., et al. (2015). *Thrombosis Research* | To compare the efficacy and safety of direct factor Xa inhibitors (rivaroxaban and apixaban) with enoxaparin for the prevention of venous thromboembolism (VTE) after total knee replacement. | Systematic Review | 2 studies, 5679 participants | Major Bleeding:<br>Pooled RR( rivaroxaban/ apixaban) = 0.72 (95% CI: 0.44-1.17) | Study Limitations =<br>☐ None<br>***Systematic Review***<br>☐ Review did not address focused clinical question<br>☐ Search was not detailed or exhaustive<br>☐ Quality of the studies was not appraised or studies were of low quality<br>☒ Methods and/or results were inconsistent across studies | |
| Russell, R. D. and M. H. Huo (2013). *Journal of Arthroplasty* | To analyze data from all of the phase III clinical trials for both newer oral direct FXa inhibitors for VTE prophylaxis in patients undergoing THAs and TKAs | Systematic Review | 11,659patients | There was a trend for an increased risk of major bleeding in patients taking rivaroxaban (OR 1.81, 95% CI 0.91–3.62, p =0.09), **but not with apixaban (p = 0.33)**<br><br>There was no difference between the oral FXa inhibitors and enoxaparin in the rates of major plus clinically relevant non-major bleeding (p = 0.91). **However, there was a trend toward fewer events in the patients taking apixaban (OR 0.8, 95% CI 0.64–1.01, p = 0.06)** and<br>there were more events in patients taking rivaroxaban (OR 1.28, 95% CI 1.04–1.59, p = 0.02). | Study Limitations =<br>☐ None<br>***Systematic Review***<br>☐ Review did not address focused clinical question<br>☐ Search was not detailed or exhaustive<br>☐ Quality of the studies was not appraised or studies were of low quality<br>☒ Methods and/or results were inconsistent across studies | |
| Squizzato, A., et al. (2015). *Thrombosis & Haemostasis* | the aim of determining: 1) the incidence of postoperative arterial | Systematic Review | 4 studies, 12,726 patients | NOACs and enoxaparin were similar at the fixed-effect model in<br>the risk of major bleeding + clinically relevant bleeding (OR 1.03; 95 %CI, 0.92, 1.15; $I^2$=38) | Study Limitations =<br>☐ None<br>***Systematic Review***<br>☐ Review did not address focused clinical question | |

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| | thrombosis (AT) in NOACs-treated and LMWH-treated patients undergoing elective TKR or THR during active treatment and during follow-up;2) the incidence of patient-relevant outcomes (i. e. prevention of major symptomatic thrombotic events and/or total mortality with minimal risk of major bleeding) with NOACs compared with standard therapy. | | | | ☐ Search was not detailed or exhaustive<br>☐ Quality of the studies was not appraised or studies were of low quality<br>☒ Methods and/or results were inconsistent across studies | |

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

## REFERENCES


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3. Forster, R. and M. Stewart (2016). "Anticoagulants (extended duration) for prevention of venous thromboembolism following total hip or knee replacement or hip fracture repair." Cochrane Database of Systematic Reviews 3: CD004179.
4. Freyburger, G., et al. (2015). "Rivaroxaban and apixaban in orthopaedics: is there a difference in their plasma concentrations and anticoagulant effects?" Blood Coagulation & Fibrinolysis 26(8): 925-933.
5. Hamidi, V., et al. (2013). "New anticoagulants as thromboprophylaxis after total hip or knee replacement." International Journal of Technology Assessment in Health Care 29(3): 234-243.
6. Ma, G., et al. (2015). "Direct factor Xa inhibitors (rivaroxaban and apixaban) versus enoxaparin for the prevention of venous thromboembolism after total knee replacement: A meta-analysis of 6 randomized clinical trials." Thrombosis Research 135(5): 816-822.
7. Ricket, A. L., et al. (2016). "Comparison of Postoperative Bleeding in Total Hip and Knee Arthroplasty Patients Receiving Rivaroxaban or Enoxaparin." Annals of Pharmacotherapy 50(4): 270-275.
8. Russell, R. D. and M. H. Huo (2013). "Apixaban and rivaroxaban decrease deep venous thrombosis but not other complications after total hip and total knee arthroplasty." Journal of Arthroplasty 28(9): 1477-1481.
9. Squizzato, A., et al. (2015). "Post-operative arterial thrombosis with non-vitamin K antagonist oral anticoagulants after total hip or knee arthroplasty." Thrombosis & Haemostasis 114(2): 237-244.

# Appendix A. GRADE criteria for rating a body of evidence on an intervention

Developed by the GRADE Working Group

***Grades and interpretations:***

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| High: Further research is very unlikely to change our confidence in the estimate of effect.<br>Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.<br>Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.<br>Very low: Any estimate of effect is very uncertain. |

***Type of evidence and starting level***

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| Randomized trial–high<br>Observational study–low<br>Any other evidence–very low |

***Criteria for increasing or decreasing level***

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| **Reductions**<br>Study quality has serious (–1) or very serious (–2) problems<br>Important inconsistency in evidence (–1)<br>Directness is somewhat (–1) or seriously (–2) uncertain<br>Sparse or imprecise data (–1)<br>Reporting bias highly probable (–1)<br>**Increases**<br>Evidence of association† strong (+1) or very strong (+2)<br>†Strong association defined as significant relative risk (factor of 2) based on consistent evidence from two or more studies with no plausible confounders Very strong association defined as significant relative risk (factor of 5) based on direct evidence with no threats to validity. |