South African National Essential Medicine List
Primary Healthcare and Adult Hospital Level of Care Medication Review Process
Component: Blood and blood forming organs

MEDICINE REVIEW

Title: Guideline adaptation of NICE Guideline "Venous thromboembolism in over 16s" for patients undergoing total hip arthroplasty or total knee arthroplasty requiring venous thromboembolism (VTE) prophylaxis

Date: 02 November 2023

INTRODUCTION

The standard of care for venous thromboembolism prophylaxis in patients undergoing total hip and total knee arthroplasty has recently been updated to rivaroxaban 10mg orally daily for 2 weeks duration in total knee replacement patients, and 5 weeks in total hip replacement patients.

This recommendation was recently ratified by the NEMLC as rivaroxaban was found to be non-inferior to LMWH, the previous standard of care, and because of the major projected cost savings in switching from LMWH to rivaroxaban[1].

In the context of the current fiscal crisis in which our health care budget has been severely cut, potential further cost-savings by using even cheaper agents was actively explored, and the option of using aspirin was investigated.

The literature search around aspirin use for this patient population was conducted and yielded few, poor quality data which were difficult to synthesise. Two high quality guidelines however, have made recommendations for use of aspirin in these patients. The NICE[5]and ASH[4] guidelines were appraised and analysed, and although both were found to be of high quality, the NICE guidelines provided more specific recommendations, and explored the hip and knee arthroplasty patient populations separately.

We used the NICE guideline[5] to formulate new recommendations for VTE prophylaxis in arthroplasty patients, incorporating aspirin for part of the duration of prophylaxis.

EXECUTIVE SUMMARY

Guideline for Adaptation: NICE Guideline "Venous thromboembolism in over 16s" (2018)

Patient population: Orthopaedic patients undergoing hip arthroplasty or knee arthroplasty requiring VTE prophylaxis
Level of care: Adult Hospital Level
Prescriber Level: Medical Doctor
Current standard of Care: LMWH recently amended to Rivaroxaban 10mg orally, daily
Motivator/reviewer name(s): Gayle Tatz, Marc Blockman
Secretariat support: Zahiera Adam
PTC affiliation: Marc Blockman (Western Cape provincial pharmacy therapeutics committee)

Adapted Guideline for Total Hip Arthroplasty Patients:

Rivaroxaban 10mg daily initiated 6-10 hours post operatively for duration of admission for a maximum of 10 days, followed by aspirin 150mg for 28 days on discharge.

Adapted Guideline for Total Knee Arthroplasty Patients:

Rivaroxaban 10mg daily initiated 6-10 hours post operatively for duration of admission for a minimum of 2 to a maximum of 7 days, followed by 150mg aspirin daily on discharge to complete 14 days of VTE prophylaxis in total (rivaroxaban followed by aspirin).

[1] NDoH Evidence Review. DOACS for VTE Prophylaxis. 12 October 2023
Adaptation of NICE Guideline "Venous thromboembolism in over 16s" for patients undergoing total hip arthroplasty or total knee arthroplasty requiring venous thromboembolism prophylaxis. November 2023. Version 1.0_30 Nov 2023_final

KEY FINDINGS

- Both the ASH (2019) and NICE (2018) guidelines scored well with AGREE II and both offered multiple pharmacological options for VTE prophylaxis in patients undergoing hip and knee arthroplasty.

- The NICE (2018) guideline offers dosing recommendations, specifies duration of therapy and considers the two patient populations separately, detailing distinct regimens for VTE prophylaxis in total hip compared with total knee arthroplasty. These factors made guideline adaptation more practical and are the reasons for choosing NICE over ASH.

- The NICE guideline found that the data for aspirin as VTE prophylaxis is of low quality which is in keeping with the reviewers' own literature search. Network meta-analyses were used to compare multiple options for prophylaxis with a separate NMA for each outcome.

	NICE Guideline	**Adapted Recommendation**
Total Hip Arthroplasty	Choose any one of: • LMWH for 10 days followed by aspirin (75 or 150 mg) for a further 28 days. • LMWH for 28 days combined with anti-embolism stockings (until discharge). • Rivaroxaban 10mg starting 6-10 hours after surgery for 5 weeks	Rivaroxaban 10mg daily initiated 6-10 hours post operatively for duration of admission for a maximum of 10 days, followed by aspirin 150mg for 28 days on discharge.
Total Knee Arthroplasty	Choose any one of: • Aspirin (75 or 150 mg) for 14 days. • LMWH for 14 days combined with anti-embolism stockings until discharge. • Rivaroxaban 10mg starting 6-10 hours after surgery for 2 weeks	Rivaroxaban 10mg daily initiated 6-10 hours post operatively for duration of admission for a minimum of 2 to a maximum of 7 days, followed by 150mg aspirin daily on discharge to complete 14 days of VTE prophylaxis in total (rivaroxaban followed by aspirin).

- Rationale for the above changes in hip arthroplasty patients:

LMWH was used in the NICE guideline for the first 10 days. In the evidence to decision, this was to mitigate the bleeding risk with aspirin which is highest in the immediate post-operative period. For our adapted recommendation, LMWH was replaced by rivaroxaban as it has been shown to be non-inferior in terms of safety and efficacy and is more cost effective. In all other respects, we have retained the recommendations as included in the NICE guideline.

- Rationale for the above changes in knee arthroplasty patients:

Considering the prolonged antiplatelet activity of aspirin together with the poor quality of data informing all guidelines on this matter, it was deemed safer to begin VTE prophylaxis with an anticoagulant other than aspirin in the initial post-operative period. This is to mitigate the potential bleeding risk with aspirin, in alignment with the recommendation for hip arthroplasty patients. The range stipulated in the guideline is to allow for individual variation in clinical course.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

Recommendation: We recommend using the option of rivaroxaban followed by aspirin for VTE prophylaxis in elective hip and knee arthroplasty patients. This is an adaptation of the 2018 NICE guideline ("Venous thromboembolism in over 16s"). This high quality guideline states that use of aspirin in this patient population is supported by low to very low certainty evidence. For this reason, our recommendation is conditional. The alternative to this prophylaxis regimen would be rivaroxaban for the full duration of prophylaxis.

For elective hip arthroplasty, we recommend:

Rivaroxaban 10mg daily initiated 6-10 hours post operatively for 10 days, followed by aspirin 150mg for 28 days on discharge

For elective knee arthroplasty, we recommend:

Rivaroxaban 10mg daily initiated 6-10 hours post operatively for duration of admission for a minimum of 2 to a maximum of 7 days, followed by 150mg aspirin daily on discharge to complete 14 days of VTE prophylaxis in total (rivaroxaban followed by aspirin).

Rationale: The NEMLC has previously made the recommendation for rivaroxaban over LMWH based on non-inferior efficacy and safety and improved cost-effectiveness of rivaroxaban for VTE prophylaxis. The NICE guideline found that there was no difference in efficacy or safety between aspirin monotherapy in knee arthroplasty or enoxaparin followed by aspirin in hip arthroplasty, compared with low molecular weight heparin monotherapy for VTE prophylaxis. Together with good evidence of efficacy and safety with use of rivaroxaban, NICE suggests any of these three treatment options at the clinician's discretion (aspirin monotherapy/enoxaparin followed by aspirin, enoxaparin monotherapy or rivaroxaban monotherapy). Our adaptation of these guidelines involved replacing the 10 days of enoxaparin preceding aspirin in total hip arthroplasty patients with rivaroxaban for cost-saving reasons, and our choice to use rivaroxaban in the initial post-operative period followed by aspirin in total knee arthroplasty patients was to mitigate the potential bleeding risk associated with aspirin identified in hip arthroplasty patients.

Level of Evidence: adaptation of a high quality guideline based on low certainty evidence

Review indicator: New data on the efficacy and/or safety of aspirin in VTE prophylaxis for arthroplasty patients.

NEMLC RECOMMENDATION (MEETING OF 30 November 2023): NEMLC supports the ERC recommendation as stated above.

Monitoring and evaluation considerations:

Research priorities

History

The National Essential Medicines List Committee (NEMLC) of South Africa, recently approved the use of rivaroxaban as venous thromboembolism prophylaxis in patients undergoing total hip and total knee arthroplasty. This has replaced the previous standard of care of low molecular weight heparin (LMWH). The medicine review and budget impact analysis informing this decision showed rivaroxaban to be non-inferior and more cost effective than LMWH.

Many international guidelines have used aspirin for thromboprophylaxis in this patient population, whether it be for the entire duration of prophylaxis post-operatively, or for the latter portion of the duration of prophylaxis. Aspirin is vastly more cost effective than either LMWH or rivaroxaban. A preliminary literature search looking at aspirin vs LMWH for VTE prophylaxis in patients undergoing hip or knee arthroplasty yielded few randomised controlled trials with all studies being of low to very low quality. Considering that two good quality guidelines were available which addressed the question of which agents may be considered for VTE

prophylaxis in patients undergoing hip or knee arthroplasty, we decided to conduct an expedited adaptation of one of the guidelines, to determine how aspirin would fit in as a prophylaxis option for these patients. The place of aspirin use in this guideline will be the focus of the review.

Rationale for selecting the NICE guideline for adaptation

Two good quality guidelines were available for patients requiring venous thromboembolism (VTE) prophylaxis after total hip or knee arthroplasty. These were:

i) the American Society of Haematology (ASH) guideline for the "Prevention of Venous Thromboembolism in Surgical Hospitalized Patients" (2019)[4] and
ii) the National Institute for Health and Care Excellence (NICE) guideline on "Venous thromboembolism in over 16s" (2019)[5].

The reason for choosing the NICE guideline is twofold. Firstly, treatment doses and durations were specified. Secondly, hip arthroplasty compared with knee arthroplasty were explored separately as two different patient populations and were found to have different treatment regimens with very different durations of therapy.

In the ASH guidelines, hip and knee arthroplasty were assessed together as a single patient population and the guideline does not specify dose or duration of treatment. We felt that the two populations (hip arthroplasty vs knee arthroplasty patients) are different in terms of their VTE risk, and that assessing them separately was necessary. Tangible dosing regimens also make adaptation simpler with the fortuitous finding that the aspirin formulations in the United Kingdom where the NICE guidelines are applicable, are similar to what is available in South Africa, further simplifying the process.

In terms of risk difference between patients undergoing total hip and total knee arthroplasty, few epidemiological studies are available. It appears from one of the largest observational cohorts however, that VTE occurs more frequently in total knee arthroplasty patients, but that this occurs most commonly within the first 2 weeks post operatively[6]. In total hip arthroplasty patients, fewer cases of VTE occur and are spread out evenly over 45 days post operatively with 4 out of 5 cases of VTE occurring within 35 days (Appendix 1). This data correlates with the duration of therapy stipulated in the guideline.

A dent in the methodological rigour of the NICE guidelines, was the use of multiple network meta-analyses (NMA) which may have allowed for the differentiation of the guidance for hip compared to knee arthroplasty patients, but was imprecise in many of the outcomes. This was balanced against the benefit of allowing for more nuanced patient care overall.

AGREE II

The NICE Guideline scored well in all 6 domains. A score of less than 30% is generally considered poor. None of the domain scoring fell into this category. The most poorly performing domain was Domain 5: Applicability.

[Domain 1: 83%; Domain 2: 61%; Domain 3: 94%; Domain 4: 89%; Domain 5: 38%; Domain 6: 83%]

NICE Guideline recommendations

The NICE Guideline makes separate recommendations for total hip arthroplasty patients and total knee arthroplasty patients requiring VTE prophylaxis.

Elective hip replacement

1.5.8 Offer VTE prophylaxis to people undergoing elective hip replacement surgery whose risk of VTE outweighs their risk of bleeding. Choose any one of:

- **LMWH[aa] for 10 days followed by aspirin[bb] (75 or 150 mg) for a further 28 days.**
- **LMWH[cc] for 28 days combined with anti-embolism stockings (until discharge).**
- **Rivaroxaban[dd].** Rivaroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement surgery or elective total knee replacement surgery. [This text is from *Rivaroxaban for the prevention of venous*

thromboembolism after total hip or total knee replacement in adults (NICE technology appraisal guidance 170).] **[2018]** This document suggests using rivaroxaban **10mg starting 6-10 hours after surgery for 5 weeks in elective hip surgery patients.**

1.5.9 Consider one of the following if none of the options in recommendation 1.5.8 can be used:

- Apixaban[ee] is recommended as an option for the prevention of venous thromboembolism in adults after elective hip or knee replacement surgery. [This text is from Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults (NICE technology appraisal guidance 245).]
- Dabigatran etexilate[ff], within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery. [This text is from Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults (NICE technology appraisal guidance 157).]

1.5.10 Consider anti-embolism stockings until discharge from hospital if pharmacological interventions are contraindicated in people undergoing elective hip replacement surgery. **[2018]**

aa At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
bb At the time of publication (March 2018), aspirin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
cc At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
dd At the time of publication (March 2018), rivaroxaban did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
ee At the time of publication (March 2018), rivaroxaban did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
ff At the time of publication (March 2018), rivaroxaban did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented.

Elective knee replacement

1.5.11 Offer VTE prophylaxis to people undergoing elective knee replacement surgery whose VTE risk outweighs their risk of bleeding. Choose any one of:

- **Aspirin[gg] (75 or 150 mg) for 14 days.**
- **LMWH[hh] for 14 days combined with anti-embolism stockings until discharge.**
- **Rivaroxaban[ii].** Rivaroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement surgery or elective total knee replacement surgery. [This text is from Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults (NICE technology appraisal guidance 170).] [2018] This document suggests using rivaroxaban **10mg starting 6-10 hours after surgery for 2 weeks in elective knee surgery patients.**

1.5.12 Consider one of the following if none of the options in recommendation 1.5.11 can be used:

- Apixaban[jj] is recommended as an option for the prevention of venous thromboembolism in adults after elective hip or knee replacement surgery. [This text is from Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults (NICE technology appraisal guidance 245).]
- Dabigatran etexilate[kk], within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery. [This text is from Dabigatran

etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults (NICE technology appraisal guidance 157).]

1.5.13 Consider intermittent pneumatic compression if pharmacological prophylaxis is contraindicated in people undergoing elective knee replacement surgery. Continue until the person is mobile. **[2018]**

gg At the time of publication (March 2018), aspirin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
hh At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
ii At the time of publication (March 2018), rivaroxaban did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
jj At the time of publication (March 2018), rivaroxaban did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
kk At the time of publication (March 2018), rivaroxaban did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented.

NMA and Evidence Quality from the NICE guideline

The evidence to decision was explicit in the NICE guideline. The evidence around aspirin use was generally considered to be poor. This was also the case in the ASH guideline and correlates with our own literature search around aspirin use in this patient population. The evidence regarding rivaroxaban use in patients undergoing total hip and total knee replacement surgery is covered in a separate NDOH review[2] and is not replicated in this document.. The NEMLC recommendation from this review supports the use of rivaroxaban over LMWH in patients undergoing total hip or knee replacement surgery for 5 and 2 weeks post operatively respectively at a dose of 10mg daily. Rivaroxaban's non-inferiority in terms of efficacy and safety, and more affordable cost were cited as the rationale by NEMLC in support of rivaroxaban over LMWH.

A NMA was used to compare different treatment regimens and a different NMA was conducted for each outcome. Interventions included: no VTE prophylaxis, pharmacological and mechanical interventions as single agents, and combination interventions of both pharmacological and mechanical interventions.

Outcomes considered included all-cause mortality, DVT (symptomatic and asymptomatic), pulmonary embolus (PE) and major bleeding. Fewer studies were included in the NICE guideline compared with the ASH guidelines, which is a limitation of the NICE guideline. Importantly, the recommendations in the ASH guideline also includes the use of aspirin as an option for VTE prophylaxis in hip and knee arthroplasty patients, which demonstrates that the final outcome of the NICE guideline was not impacted by the inclusion of fewer studies.

Total Hip Arthroplasty

Table 43 in the NICE guideline (figure 1) depicts the clinical evidence summary for total hip arthroplasty patients comparing a standard dose of dalteparin (5000IU daily) for 5 weeks with dalteparin for 10 days followed by aspirin 81mg daily for 28 days. The GRADE assessment of the quality of the data was low for the outcomes of all-cause mortality, fatal PE, major bleeding, clinically relevant other major bleeding and wound infection. It was very low for the outcome of PE.

There is no DVT outcome included. This has been noted as a limitation of the guideline and this was because it was not included in the DVT NMA. This outcome was not reported as the informing trial using this particular regimen reported only on proximal DVTs and not on symptomatic and asymptomatic DVTs which all of the other trials had reported on. DVT (symptomatic and asymptomatic) outcome was assumed to be the same as that for the outcome "proximal DVT" which was reported in the included trial and there was therefore no reported difference between intervention and comparator.

[2] NDoH Evidence Review. DOACS for VTE Prophylaxis. 12 October 2023
Adaptation of NICE Guideline "Venous thromboembolism in over 16s" for patients undergoing total hip arthroplasty or total knee arthroplasty requiring venous thromboembolism prophylaxis. November 2023. Version 1.0_30 Nov 2023_final

Risk differences were not estimable for all-cause mortality, PE and major bleeding as there were zero events in the intervention arm. The population concerned in the evidence used was a North American population with a mean age of 57.8 years and a male:female ratio of 1.3:1.

Table 43: Clinical evidence summary: LMWH (standard dose; extended duration) versus LMWH (standard dose; standard duration) followed by aspirin (extended duration)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with LMWH followed by Aspirin (extended duration)	Risk difference with LMWH (extended duration) (95% CI)
All-cause mortality	785 (1 study) 90 days	LOW[b] due to imprecision	Peto OR 7.12 (0.14 to 358.94)	0 per 1000	-[a]
PE	778 (1 study) 90 days	VERY LOW[b,c] due to risk of bias, imprecision	Peto OR 7.1 (0.74 to 68.48)	0 per 1000	-[a]
Fatal PE	785 (1 study) 90 days	LOW[b] due to imprecision	Not estimable4	Not estimable[a]	0 fewer per 1000 (from 0 fewer to 0 more)[d]
Major bleeding	785 (1 study) 90 days	LOW[b] due to imprecision	Peto OR 7.12 (0.14 to 358.94)	0 per 1000	-[a]
Clinically relevant non-major bleeding	785 (1 study) 90 days	LOW[b] due to imprecision	Peto OR 1.88 (0.38 to 9.38)	5 per 1000	5 more per 1000 (from 3 fewer to 4 more)
Wound infection	785 (1 study) 90 days	LOW[b] due to imprecision	RR 0.8 (0.35 to 1.83)	31 per 1000	6 fewer per 1000 (from 20 fewer to 26 more)

a Absolute effect could not be calculated due to zero events in the intervention arm
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
c Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
d Zero events in both arms. Risk difference calculated in Review Manager.

Figure 1

Table 63 (figure 2) depicts the clinical evidence summary for total hip arthroplasty patients comparing unfractionated heparin with aspirin. This is included as it was a component of the meta-analysis but as an individual finding, is not relevant to this review.

Table 63: Clinical evidence summary: UFH versus aspirin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Aspirin	Risk difference with UFH (95% CI)
DVT (symptomatic and asymptomatic)	37 (1 study) 7 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.24 (0.05 to 1.13)	333 per 1000	253 fewer per 1000 (from 317 fewer to 43 more)
PE	37 (1 study) 7 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	Peto OR 0.10 (0 to 5.16)	83 per 1000	74 fewer per 1000 (from 83 fewer to 236 more)
Fatal PE	37 (1 study) 7 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.76 (0.05 to 11.39)	83 per 1000	20 fewer per 1000 (from 79 fewer to 866 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Figure 2

Total Knee Arthroplasty

Table 86 (figure 3) depicts the clinical evidence summary in total knee arthroplasty patients comparing enoxaparin 40mg daily with aspirin 100mg daily as prophylaxis. Only the outcomes of DVT and PE are available although the relative effect between the intervention and comparator for the outcome of PE is not estimable because of the extremely low event rates (zero in both arms). There was very serious imprecision, indirectness and risk of bias surrounding both results and quality of evidence was very low on both counts.

Table 86: Clinical evidence summary: LMWH (standard dose; standard duration) versus aspirin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Aspirin	Risk difference with LMWH (standard dose) (95% CI)
DVT (symptomatic and asymptomatic)	222 (1 study) 28 days	VERY LOW[a,c] due to risk of bias, imprecision	RR 0.76 (0.4 to 1.46)	164 per 1000	39 fewer per 1000 (from 98 fewer to 75 more)
PE	222 (1 study) 28 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	Not estimable[d]	Not estimable[d]	0 fewer per 1000 (from 20 fewer to 20 more)[d]

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

d Zero events in both arms of one of the studies included. Risk difference calculated in Review Manager.

Figure 3

Table 113 (figure 4) shows the clinical evidence summary in total knee arthroplasty patients comparing rivaroxaban 10mg daily with aspirin 100mg daily as prophylaxis. The risk difference of PE was once again not estimable due to zero events occurring in both arms and the GRADE was considered very low. The risk of DVT (symptomatic and asymptomatic was low with rivaroxaban compared with aspirin at 134 fewer events per 1000 (134 fewer to 67 fewer) with a high quality of evidence rating on GRADE. It is important to note that not included in the guideline, is the breakdown of symptomatic vs asymptomatic DVTs. There were 2 symptomatic DVTs in the aspirin arm and 0 in the rivaroxaban arm. The committee noted the dose used for aspirin in the evidence represented a non-standard dose for the UK at 100mg per day and they stipulated that clinicians can decide whether to use 75mg or 150mg.

Table 113: Clinical evidence summary: Rivaroxaban versus aspirin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Aspirin	Risk difference with Rivaroxaban (95% CI)
DVT (symptomatic and asymptomatic)	212 (1 study) 28 days	HIGH	RR 0.18 (0.05 to 0.59)	164 per 1000	134 fewer per 1000 (from 67 fewer to 155 fewer)
PE	212 (1 study) 28 days	VERY LOW[a,c,d] due to risk of bias, indirectness, imprecision	Not estimable[b]	Not estimable[b]	0 fewer per 1000 (from 20 fewer to 20 more)[b]

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b Zero events in both arms. Risk difference calculated in Review Manager.

c Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

d Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Figure 4

Evidence to Decision: NICE Guideline

Total Hip Arthroplasty

Below is an excerpt justifying the choice of regimen for hip arthroplasty patients.

"The top ranked intervention for the clinical outcomes of PE and major bleeding was a combined pharmacological option of LMWH initially, followed by aspirin. The committee and orthopaedic subgroup discussed the current concerns in regards to the bleeding risk associated with aspirin, especially when used soon after surgery (when bleeding risk is highest). However they agreed that the use of aspirin after a 10-day course of LMWH would take into account the high early bleeding risk whilst providing clinical benefit in terms of the evaluated outcomes of PE and major bleeding. The durations for LMWH (10 days) and aspirin (28 days) are based on the evidence evaluated in the clinical trials."

Total Knee Arthroplasty

The evidence to decision process for use of aspirin in total knee arthroplasty patients for VTE prophylaxis was based on the fact that aspirin appeared to be non-inferior to LMWH and performed neither well nor poorly in

comparison to other interventions. Rivaroxaban was rated highest. The guideline stated that "The inclusion of aspirin and LMWH combined with anti-embolism stockings (until discharge) in the recommendation was primarily based on the results from the economic model (see 'Trade-off between net clinical effects and costs' section for further discussion). The durations of the interventions were based on the durations presented in the relevant clinical trials."

Contextualising within South African Health Care system

The standard of care for VTE prophylaxis is LMWH which has recently (2020-23 review cycle) been changed to rivaroxaban given the non-inferior efficacy, similar safety profile, and cost-effectiveness. While evidence supports a comparable efficacy and safety profile between apixaban and rivaroxaban; based on current pricing, rivaroxaban is the more cost-effective option.

Aspirin has been identified in the NICE guideline discussed, as being an option for both hip and knee arthroplasty patients, the use of which differs between these two groups. In the South African context, we suggest adapting the NICE guideline in the following way:

Total Hip Arthroplasty Patients

Rivaroxaban 10mg daily initiated 6-10 hours post operatively for duration of admission for a maximum of 10 days, followed by aspirin 150mg for 28 days on discharge.

Total Knee Arthroplasty Patients

Rivaroxaban 10mg daily initiated 6-10 hours post operatively for duration of admission for a minimum of 2 to a maximum of 7 days, followed by 150mg aspirin daily on discharge to complete 14 days of VTE prophylaxis.

Rationale: Adaptation of NICE Guideline for the EML

Total Hip Arthroplasty Patients

LMWH was used in the NICE guideline for the first 10 days. For the purposes of the EML, we have taken the decision to replace LMWH with rivaroxaban as it has been shown to be non-inferior in terms of safety and efficacy and is more cost effective. In all other respects, our recommendation for the EML is the same as the NICE guideline.

Total Knee Arthroplasty Patients

In the NICE evidence to decision for VTE prophylaxis in patients undergoing total hip arthroplasty, allowance was made for the initial use of LMWH in the immediate post-operative period as bleeding risk with aspirin use was highest at this time. The same consideration was not given for patients undergoing total knee arthroplasty. Considering the prolonged antiplatelet activity of aspirin together with the poor quality of data informing all guidelines on this matter, it was deemed safer to begin VTE prophylaxis with an anticoagulant other than aspirin in the initial post-operative period. For the EML guidance, we opted for rivaroxaban as the anticoagulant of choice as it is cheaper than LMWH. With the exception of patients who develop complications post-surgery, patients who have undergone total knee arthroplasties are not expected to remain admitted for prolonged periods and it is reasonable to give rivaroxaban as VTE prophylaxis in hospital, followed by aspirin on discharge. The range stipulated in our recommendation is to allow for individual variation in clinical course.

References

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Appendices

Appendix 1

From Sumama et al.[6] showing the timing of venous thromboembolic events after total hip and total knee replacement in the first 90 days post-operatively.

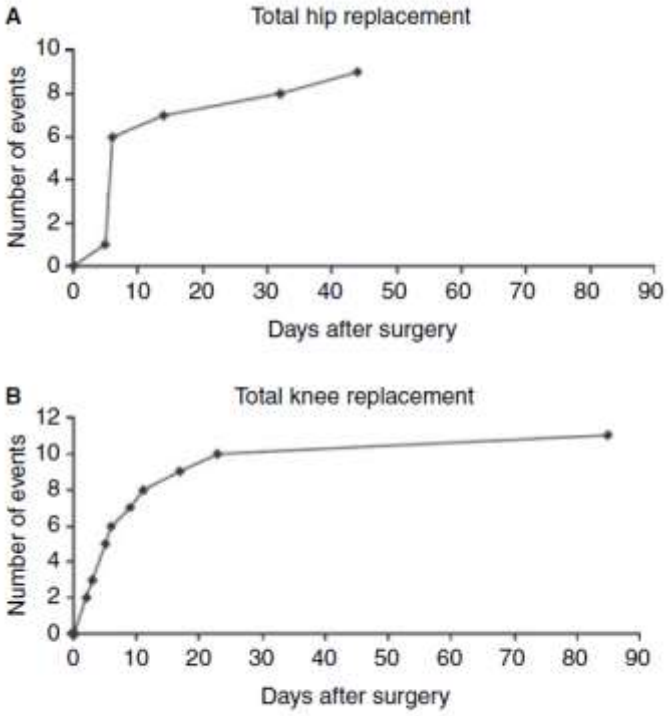

Fig. 1. Time to occurrence of venous thromboembolism after the surgical procedure (day 0).