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: Direct oral anticoagulants (DOACs) for venous thromboembolism (VTE) prophylaxis in hospitalised, adult patients

EXECUTIVE SUMMARY

Date:	2 October 2023
Medicine (INN):	Rivaroxaban
Medicine (ATC):	Antithrombotic agents (B01A, B01AF01, B01AE07, B01AF02)
Indication (ICD10 code):	Z29.2 + (I80.0-3/I80.8-9/I81/I82.0-3/I8.8-9/I26.0/I26.9)
Patient population:	Hospitalised adult patients at risk of venous thromboembolism requiring prophylaxis

Prevalence of condition:

- The majority (77-97%) of hospitalised medical and surgical adult patients in South Africa are at moderate to high risk of venous thromboembolism and require chemoprophylaxis.[1,2]
- The burden of infectious diseases including HIV and TB appear to contribute to this high risk of venous thromboembolism in the South African setting.[3]

Level of Care:	Adult Hospital Level
Prescriber Level:	Medical Doctor
Current standard of Care:	Enoxaparin (LMWH) 40mg by subcutaneous injection given daily
Efficacy and safety estimates:	DOACs vs LMWH

Hospitalised medically ill adult patients

- **no difference in risk of mortality,** RR 0.64 (95% CI 0.21 to 1.98)
- **similar risk of VTE** (DVT: RR 1.03 (95% CI 0.34 to 3.08), PE: RR 1.01 (95% CI, 0.29 to 3.53)
- **small increase in the risk of major bleeding,** 4 vs 2 major bleeds per 1000 patients treated, NNTH 500, RR 1.70; (95% CI, 1.02 to 2.82)

Hospitalised surgical adult patients post total hip or total knee arthroplasty

- **similar risk in mortality**, RR 0.94 (95% CI 0.53 to 1.66)
- **no difference in risk of symptomatic PE,** RR 0.74 (95% CI 0.50 to 1.10)
- **decreased risk of symptomatic DVT**, RR 0.56 (95% CI 0.39 to 0.79)
- **similar risk of major bleeding**, RR 1.03 (95% CI 0.79 to 1.35)
- **no difference in risk of reoperation,** RR 1.43 (95% CI 0.75 to 2.71)

Motivator/reviewer name(s):	Gayle Tatz, Marc Blockman
Secretariat support:	Zahiera Adam
PTC affiliation:	Marc Blockman (Western Cape provincial pharmacy therapeutics committee)

1. Rocher WD, Page T, Rocher M, Nel D. Venous thromboembolism risk and prophylaxis prescription in surgical patients at a tertiary hospital in Eastern Cape Province, South Africa. South African Medical Journal. 2019 Mar 7;109(3):178-81.
2. Wehmeyer A, Coetzee R, McCartney J. Venous thromboembolism risk assessment and prophylaxis in hospitalised medical patients in the Cape Town metropole, South Africa. S Afr Med J. 2022 Feb 1;112(2):13506. PMID: 35139994.
3. Moodley P, Martinson NA, Joyimbana W, Otwombe KN, Abraham P, Motlhaoleng K, Naidoo VA, Variava E. Venous thromboembolic disease in adults admitted to hospital in a setting with a high burden of HIV and TB. African Journal of Thoracic and Critical Care Medicine. 2021 Sep 1;27(3):99-105.

KEY FINDINGS:

- We conducted a review of current relevant, high quality practice guidelines and the systematic reviews which informed their recommendations regarding the prevention of venous thromboembolism (VTE) - encompassing both deep vein thrombosis (DVT) and pulmonary embolism (PE) - in adult, hospitalised patients at risk.

- We used AGREE II to appraise the American Society of Haematology (ASH) 2018 guideline for prophylaxis in medical patients, the ASH 2019 guideline for prophylaxis in surgical patients and National Institute for Health Care Excellence (NICE) 2018 guidelines for VTE prophylaxis. All were found to be of good quality.

HOSPITALISED, ADULT, MEDICALLY ILL PATIENTS:

- For the population of medically ill patients requiring VTE prophylaxis, the ASH 2018 guidelines included 3 randomised controlled trials (RCTs) which our AMSTAR appraisal showed to be of good quality. Two of these three comprised the total evidence for the NICE guidelines and thus the ASH 2018 guideline was summarised and reported as it included an additional RCT. We ran an updated search from 1 January 2019 to 30 September 2023, but found no new trials.

- The ASH review found that in hospitalised, medically ill patients using VTE prophylaxis:
  - There is **no difference in risk of mortality** between direct oral anticoagulants (DOACs) and low molecular weight heparin (LMWH), RR 0.64 (95% CI 0.21 to 1.98) with **high-certainty evidence**
  - There is a **similar risk of VTE** (DVT: RR 1.03 (95% CI 0.34 to 3.08); PE: RR 1.01 (95% CI, 0.29 to 3.53) with **moderate-certainty evidence**.
  - The use of a DOAC was associated with a **small increase in the risk of major bleeding** (RR 1.70; 95% CI, 1.02-2.82). Numbers needed to harm = 500 (95% CI 250-∞) and does not translate into an increased mortality risk. This risk may be considered **trivial in the context of major cost-savings** implicated in the recommendation of use of a DOAC in place of LMWH.

HOSPITALISED, SURGICALLY ILL PATIENTS:

- There is a paucity of evidence which compares outcomes associated with using either LMWH or DOACs for patients undergoing major surgery. The sub-population of surgical patients who have undergone hip or knee arthroplasty however, has been extensively studied.

- The ASH 2019 guideline identified 1 systematic review which included 22 studies that fulfilled their inclusion criteria and an additional 16 studies in their update of the systematic review. All studies were RCTs which involved a patient population who had undergone hip or knee replacement and received thromboprophylaxis with either LMWH or a DOAC.

- The ASH review found that in hospitalised, surgically ill patients who had undergone **total hip or total knee arthroplasty** using DOACS vs LMWH for VTE prophylaxis:
  - There is **similar risk in mortality** between DOACs and LMWH, RR 0.94 (95% CI 0.53 to 1.66) with **moderate-certainty** evidence.
  - There is **no difference in risk of symptomatic PE**, RR 0.74 (95% CI 0.50 to 1.10) with **moderate-certainty** evidence.
  - There is **decreased risk of symptomatic DVT**, RR 0,56 (95% CI 0.39 to 0.79) with **high-certainty** evidence.
  - There is **similar risk of major bleeding**, RR 1.03 (95% CI 0.79 to 1.35) with **high-certainty** evidence.
  - There is **no difference in risk of reoperation**, RR 1.43 (95% CI 0.75 to 2.71) with **moderate-certainty** evidence.

- Overall, DOACS have similar mortality and VTE outcomes as LMWH when used for the prevention of VTE in medically ill patients and surgical patients who have undergone total hip or total knee arthroplasty procedures. In medically ill patients, the increased risk of major bleeding with DOACs may be considered trivial in the context of major cost savings.

- Rivaroxaban is currently the only DOAC for which a cost-analysis has been performed as it is on government contract; and other DOACs are currently more expensive. There are massive projected cost-savings with use of rivaroxaban over enoxaparin and thus **this recommendation is specific to rivaroxaban**.

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: Based on this evidence review, the PHC/Adult Hospital Level Committee recommends that direct oral anticoagulants (DOACs) be used for the prevention of venous thromboembolism (VTE) in medically ill, hospitalised, adult patients and for adult patients who require VTE prophylaxis post total hip or total knee arthroplasty.
(Strong: No difference in benefits with trivial increase in major bleeding offset by projected major cost-savings)

Rationale: There is clear evidence of non-inferiority of DOACs (rivaroxaban and apixaban) compared to LMWH for preventing VTE in the above patient populations. In medically ill, hospitalised, adult patients requiring VTE prophylaxis, there was a trivial increase in major bleeding that does not translate into increased mortality and is offset by major cost-savings. Major cost-savings are specific to rivaroxaban at the current contract price, and this recommendation is therefore specific to rivaroxaban within the DOAC class.
Level of Evidence: *Moderate to high certainty*
Review indicator: High quality evidence of a clinically relevant benefit or reduction of harms; new cost data for rivaroxaban, apixaban or LMWH

NEMLC RECOMMENDATION (12 October 2023): NEMLC supported the ERC's recommendation on the use of direct oral anticoagulants (DOACs) for the prevention of venous thromboembolism (VTE) in medically ill, hospitalised, adult patients and for adult patients who require VTE prophylaxis post total hip or total knee arthroplasty. This recommendation excludes the subset of patients (*hospitalised patients with trauma-related operative or non-operative extremity fractures or trauma-related pelvic or acetabular fractures at risk of VTE')* in whom aspirin is recommended over LMWH (refer to Evidence summary on aspirin for VTE prophylaxis).

Monitoring and evaluation considerations

Research priorities

NAME OF AUTHOR(S)/MOTIVATOR(S) AND CONFLICT OF INTEREST DECLARATION

Current, updated review: Gayle Tatz[1], Marc Blockman[1]
*The above authors have no conflicts of interest to declare.
(Original Review: Roland van Rensburg[2], Veshni Pillay-Fuentes Lorente[2], Tamara Kredo[3], Nqoba Tsabedze[4], Marc Blockman[1])

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[4]University of the Witwatersrand; Adult Hospital Level Committee, National Department of Health, South Africa; Charlotte Maxeke Johannesburg Academic Hospital

1. Introduction/ Background

Cardiovascular disease remains amongst the top three causes of death globally.[1] Within the causes of cardiovascular related deaths, venous thromboembolism (VTE) has high mortality rates and commonly presents as deep vein thrombosis (DVT) or pulmonary embolism (PE).[1–3] Hospitalised patients are at higher risk of developing VTE.[3] A USA study found that per 10 000 person-years, the average annual age- and sex-adjusted incidence of in-hospital VTE was 960.5 (95% confidence interval, 795.1-1125.9) as compared to 7.1 (95% confidence interval, 6.5-7.6) in community residents.[4] This reflects a 135 times greater risk of VTE when hospitalised.

The current standard of care for VTE prevention is low molecular weight heparin (LMWH).[5] Enoxaparin, a LMWH commonly used in South Africa, acts by binding to antithrombin III, leading to the inhibition of factor Xa. This ultimately leads to the decrease of fibrin formation and/or expansion.

Direct oral anticoagulants (DOACs) have been on the international market since 2008, with dabigatran being the first to be marketed as a direct thrombin inhibitor. Dabigatran etexilate, a prodrug, is converted to an active metabolite dabigatran which binds to thrombin hence altering the clotting cascade. It has a quick onset of action (approximately 2 hours) and could potentially not require concomitant administration of parenteral heparin.[6, 7] However, rivaroxaban was first marketed in 2008, followed by apixaban in 2011. Both drugs are inhibitors of factor Xa and do not require initial administration of parenteral heparin.

DOACs have been considered as an alternate to LMWH in the prevention of VTE, as they are available in oral formulations, increasing ease of administration and decreasing potential complications associated with the parenteral route. Major bleeding is a concern with the administration of both the DOACs and heparins, although the risk is attenuated with prevention compared to treatment doses. Reversal agents for some heparins are readily available and affordable in South Africa, but reversal agents for DOACs are expensive and are not readily available in South Africa.

In South Africa, DOACs have become progressively more affordable and rivaroxaban is currently significantly less costly than enoxaparin dose for dose. Due to the profound cost-savings that could be incurred by using rivaroxaban in place of enoxaparin, it would be important to evaluate the role of DOACs as an alternate therapy, or as a potentially new standard of care for VTE prevention. This evaluation assessed the clinical benefits and harms as well as costs in an evidence-based manner, compared to our current standard practice.

2. Purpose/Objective i.e. PICO question:

Should DOACs be used in favour of LMWH for the prevention of VTE in hospitalised adult patients?

Population – Hospitalised, adult patients at risk of VTE
Intervention – DOACs (rivaroxaban, apixaban and dabigatran)
Comparator – Heparin/LMWH
Outcome - Venous thrombosis (deep vein thrombosis – DVT, and pulmonary embolism – PE), embolic events, mortality, major bleeds
Study design - A review of clinical practice guidelines with high quality systematic reviews.

3. Methods:

Health Technology Assessments (HTAs): We conducted a search in September 2023 for HTAs on the following electronic databases: The International Network of Agencies for Health Technology Assessment (INAHTA), Epistemonikos and Cochrane library, using a simple search with broad search terms.

Guidelines: A search for current, relevant practice guidelines with available systematic reviews that informed them was conducted on the following websites: National Institute for Health Care Excellence (NICE), American Society of Haematology (ASH), American Heart Association (ACA), Canadian Agency for Drugs and Technologies in Health (CADTH) and the Scottish Medicines Consortium (SMC). Terms included were "DOAC, VTE and heparin."

The search and screening of eligible HTAs and guidelines were independently reviewed by two reviewers considering the following factors: most recent, best quality, include most evidence (i.e. relevant trials). All included studies are reported in Table 4 Table of excluded evidence, and the excluded studies are described with reason for exclusion below (Table 1).

Critical appraisal: The identified systematic reviews were assessed using the AMSTAR appraisal tool. Related guidelines were appraised using the AGREE II appraisal tool. For the included evidence, we checked the last search dates and then conducted a comprehensive electronic search in two databases (PubMed and CENTRAL) up to 30 September 2021. The search strategy is reported in Appendix 1. All identified records were screened by title and abstract for eligibility by a single reviewer on the COVIDENCE software. All eligible studies for full text review were evaluated by two reviewers for full data extraction.

Excluded guidelines and their related systematic reviews:

Table 1. Table of excluded evidence

Author, date	Patient Population	Type of document	Reason for exclusion
Sterne JAC, et al (2017)[8]	Hospitalised medically ill adults	HTA	Search only done up until September 2014. The review authors did not explain their selection of the study designs for inclusion in the review, and did not investigate for publication bias
NICE (originally published 2018, updated 2019)[9]	Hospitalised, ill adults	Guideline (with report of systematic reviews of RCTs)	Only included 2 RCTs comparing rivaroxaban and apixaban to LMWH, both of which were included in the ASH guideline.
NICE (originally published 2009, updated 2012)[10]	Hospitalised adults post total hip or knee arthroplasty	Guideline (with report of systematic reviews of RCTs)	Only included 6 RCTs comparing rivaroxaban only to enoxaparin, all of which were included in the ASH guideline.

Evidence synthesis

One HTA was identified but the last search date in the HTA was September 2014. The study was excluded from the review because, 1) the review authors did not explain their selection of the study designs for inclusion in the review, and 2) did not investigate for publication bias. We found four clinical practice guidelines: NICE 2018 guideline for prophylaxis in hospitalised adult patients, the NICE guideline for hospitalised adults undergoing hip or knee arthroplasty, the ASH 2018 guideline for prophylaxis in medical patients and the ASH 2019 guideline for prophylaxis in surgical patients[9-12]. All guidelines' overall quality of evidence as per AGREE II was rated 6/7. They were downgraded for inadequate reporting on stakeholder involvement.

<u>Hospitalised, medically ill, adult patients:</u>

The NICE guideline was excluded since it included only 2 RCTs, both of which were included in the ASH guideline.
The ASH guideline included a systematic review of 3 RCTs and was included in this review. Rivaroxaban and apixaban were assessed; no studies on dabigatran were available. We conducted an updated search from 1 January 2019 to 30 September 2021 for RCTs. Four-hundred and thirty-eight articles were identified, four articles were duplicate publications, and 434 articles were screened by title and abstract. Two articles were selected for full text review. We identified one eligible trial; however, it was the publication of the systematic review and meta-analysis that informed 2018 ASH guidelines, and was therefore already incorporated in the 2018 ASH guideline.

Surgical adult patients undergoing total hip or knee arthroplasty:

The NICE guideline was excluded as it was published in 2009 and last updated in2012. It only included 6 RCTs, all of which were included in the more recent ASH 2019 guideline. The ASH guideline included a total of 22 studies from one systematic review and an additional 16 studies after a search of the literature for more recent studies. All included studies were RCTs. Five studies assessed the effects of dabigatran versus enoxaparin, 15 studies assessed the effects of rivaroxaban versus enoxaparin, 4 studies assessed the effects of apixaban, 5 assessed the effects of darexaban and edoxaban and 4 studies assessed the effects of other DOACs. Thirty-four studies reported on mortality, 33 no nonfatal PEs and 30 on symptomatic DVTs (distal and proximal estimates pooled)

Effectiveness of the intervention: Hospitalised, medically ill, adult patients
Follow up range 10-14 days.

1. *Mortality*

From the available evidence, the use of a DOAC (rivaroxaban or apixaban) instead of LMWH for patients at risk of VTE does not impact mortality at 10 to 14-day follow up. The reported risk ratio (RR) for mortality is 0.64; 95% CI, 0.21-1.98. The anticipated absolute effects demonstrated a risk difference with DOACs to be 0 fewer per 1000 patients (95% CI, 1 fewer to 1 more). The evidence was assessed as high certainty evidence.

2. *Venous thrombosis (DVT and PE), and embolic events*

From the available evidence, the use of a DOAC (rivaroxaban or apixaban) instead of LMWH for patients at risk of VTE does not impact the risk of VTE at 10 to 14-day follow up. The reported RR for the development of DVT is 1.03; 95% CI, 0.34-3.08, and for PE the RR is 1.01; 95% CI, 0.29-3.53. The anticipated absolute effects demonstrated a risk difference with DOACs to be 0 fewer per 1000 patients (95% CI, 1 fewer to 2 more) for DVT, and 0 fewer per 1000 patients (95% CI, 1 fewer to 3 more) for PE. The evidence was assessed as moderate certainty evidence. Embolic events were not reported on.

Harms of the intervention: Hospitalised, medically ill, adult patients
Follow up range 10-14 days.

3. *Major bleeds*

Major bleeds were defined according to the International Society on Thrombosis and Haemostasis (ISTH)[14] as follows: a) Fatal bleeding, and/or b) Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra- articular or pericardial, or intramuscular with compartment syndrome, and/or c) Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.

From the available evidence, the use of a DOAC (rivaroxaban or apixaban) instead of LMWH for patients at risk of VTE was found to impact the risk of major bleeding at 10 to 14-day follow up. The reported RR for the development of major bleeding is 1.7; 95% CI, 1.02-2.82. The anticipated absolute effects demonstrated a risk difference of 1 more major bleed per 1000 patients administered a DOAC compared to LMWH (95% CI, 0 to 4 more). The absolute risk difference was 0.2% (0.4% with a DOAC compared to 0.2% with LMWH). The numbers needed to harm is therefore 500; i.e. 500 patients need to be treated with a DOAC for 1 patient to experience an additional major bleed, compared to LMWH. The evidence was assessed as high certainty evidence.

Table 2: Summary of findings table: hospitalised, medically ill, adult patients from ASH 2018 guideline.

Author(s): Ignacio Neumann, Juan Jose Yepes-Nuñez, Wojtek Wiercioch, Holger Schünemann

Question: Any DOAC compared to LMWH for VTE prophylaxis in acutely ill hospitalized medical patients

Setting: Inpatient

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	any DOAC	LMWH	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: range 10 days to 14 days; assessed with: VTE related death)												
3	randomised trials	not serious	not serious	not serious	not serious	none	5/9914 (0.1%)	8/9986 (0.1%)	**RR 0.64** (0.21 to 1.98)	**0 fewer per 1,000** (1 fewer to 1 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Pulmonary Embolism – representing the moderate marker state (follow up: range 10 days to 14 days; assessed with: Non-fatal PE)												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	11/9911 (0.1%)	11/9984 (0.1%) 0.4% [b]	**RR 1.01** (0.29 to 3.53)	**0 fewer per 1,000** (1 fewer to 3 more) **0 fewer per 1,000** (3 fewer to 10 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Proximal Deep Vein Thrombosis – representing the moderate marker state (follow up: range 10 days to 14 days; assessed with: Symptomatic DVT)												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	11/9914 (0.1%)	11/9986 (0.1%) 0.2% [c,d]	**RR 1.03** (0.34 to 3.08)	**0 fewer per 1,000** (1 fewer to 2 more) **0 fewer per 1,000** (1 fewer to 4 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Distal Deep Vein Thrombosis – representing the moderate distal DVT marker state (follow up: range 10 days to 14 days; assessed with: Symptomatic DVT)												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	11/9914 (0.1%)	11/9986 (0.1%) 0.6% [c,d]	**RR 1.03** (0.34 to 3.08)	**0 fewer per 1,000** (1 fewer to 2 more) **0 fewer per 1,000** (4 fewer to 12 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Major bleeding (follow up: range 10 days to 14 days)												
3	randomised trials	not serious	not serious	not serious	not serious	none	41/10894 (0.4%)	24/10927 (0.2%) 1.2% [e]	**RR 1.70** (1.02 to 2.82)	**2 more per 1,000** (0 fewer to 4 more) **8 more per 1,000** (0 fewer to 22 more)	⊕⊕⊕⊕ HIGH	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Serious Imprecision. The relative estimate of effect is compatible with important harm and important benefit for the intervention that probably crosses the relevant decision threshold.

b. Guijarro (2014) reports on the incidence of PE in acutely ill hospitalized medical patients (n=1,148,301) based on findings from the Spanish National Discharge Database from October 2005 to September 2006 (retrospective database study)
c. Guijarro (2014) reports on the incidence of DVT in acutely ill hospitalized medical patients (n=1,148,301) based on findings from the Spanish National Discharge Database from October 2005 to September 2006 (retrospective database study)
d. We applied the assumption that approximately 20% of symptomatic DVTs are proximal, 80% are distal and 100% of each is of moderate severity.
e. Spencer (2014) reported on incidence rates of major bleeding in older adults based on a community-based study (n=1223) (prospective and retrospective)

Evidence quality:
The quality of evidence for the outcomes of mortality and major bleeding was assessed as high certainty evidence. VTE (DVT and PE) was assessed to be of moderate certainty evidence. The overall quality of the guideline was high and rated 6/7 using the AGREE II tool.

Effectiveness of the intervention: Surgical, adult patients undergoing total hip or knee arthroplasty
Follow up range: 10-35 days.

1. Mortality

There is similar risk in mortality between DOACs and LMWH for patients requiring thromboprophylaxis. The reported risk ratio (RR) for mortality is RR 0.94 (95% CI 0.53 to 1.66). The anticipated absolute effect demonstrated a risk difference with DOACs to be 0 fewer deaths (1 fewer to 1 more) per 1000 patients. The evidence was assessed to be of moderate certainty.

2. Deep Vein Thrombosis

There is a reduction in the risk of symptomatic DVT between patients at risk of VTE who use a DOAC compared with LMWH. The reported RR for the development of DVT is RR 0.56 (95% CI 0.39 to 0.79). The anticipated absolute effect demonstrated a risk difference with DOACs to be 3 fewer per 1000 patients (4 fewer to 1 fewer) for DVT. The evidence was assessed to be of moderate certainty.

3. Pulmonary Embolism

There is no difference in the risk of symptomatic PE between patients at risk of VTE who use a DOAC compared with LMWH. The reported RR for the development of PE is RR 0.74 (95% CI 0.50 to 1.10). The anticipated absolute effect demonstrated a risk difference with DOACs to be 1 fewer (3 fewer to 1 more) per 1000 patients. The evidence was assessed to be of high certainty.

Harms of the intervention: Surgical, adult patients undergoing total hip or knee arthroplasty
Follow up range: 10-35 days.

4. Major bleeds

Major bleeds were defined according to the International Society on Thrombosis and Haemostasis (ISTH)[14] as follows: a) Fatal bleeding, and/or b) Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra- articular or pericardial, or intramuscular with compartment syndrome, and/or c) Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.

There is similar risk of major bleeding between patients at risk of VTE who use a DOAC compared with LMWH. The reported RR for the development of major bleeding is RR 1.03 (95% CI 0.79 to 1.35). The anticipated absolute effect demonstrated a risk difference with DOACs to be 0 fewer (2 fewer to 3 more) per 1000 patients. The evidence was assessed to be of moderate certainty.

5. Reoperation

There is no difference in the risk of reoperation between patients at risk of VTE who use a DOAC compared with LMWH. The reported RR for the occurrence of reoperation is RR 1.43 (95% CI 0.75 to 2.71). The anticipated absolute effect demonstrated a risk difference with DOACs to be 0 fewer (0 fewer to 2 more) per 1000 patients. The evidence was assessed to be of moderate certainty.

Table 3: Summary of findings Table: hospitalised surgical patients undergoing total hip or knee arthroplasty from ASH 2019 guideline.

Author(s): Ignacio Neumann, Itziar Etxeandia-Ikobaltzeta, Gian Paolo Morgano, Wojtek Wiercioch
Question: DOACs compared to LMWH for patients undergoing total hip or knee arthroplasty
Setting: inpatient
Bibliography: American Society of Hematology 2019 Guidelines for Management of Venous Thromboembolism: Prevention of Venous Thromboembolism in Surgical Hospitalized Patients

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DOACs	LMWH	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: range 10 days to 35 days)												
34	randomised trials	not serious	not serious	not serious	serious [b]	none	35/24826 (0.1%)	21/17020 (0.1%)	**RR 0.94** (0.53 to 1.66)	**0 fewer per 1,000** (from 1 fewer to 1 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Symptomatic Pulmonary Embolism - representing the moderate marker state (follow up: range 10 days to 35 days; assessed with: non fatal Symptomatic PE)												
33	randomised trials	not serious [c]	not serious	not serious	serious [b]	none	62/24692 (0.3%)	49/16942 (0.3%)	**RR 0.74** (0.50 to 1.10)	**1 fewer per 1,000** (from 1 fewer to 0 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
								0.6% [d]		**1 fewer per 1,000** (from 3 fewer to 1 more)		
Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state (follow up: range 10 days to 35 days; assessed with: any Symptomatic DVT)												
30	randomised trials	not serious [c]	not serious	not serious	not serious	none	89/23196 (0.4%)	98/16728 (0.6%)	**RR 0.56** (0.39 to 0.79)	**3 fewer per 1,000** (from 4 fewer to 1 fewer) [f]	⊕⊕⊕⊕ HIGH	CRITICAL
								0.6% [e]		**3 fewer per 1,000** (from 4 fewer to 1 fewer)		
Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state (follow up: range 10 days to 35 days; assessed with: any Symptomatic DVT)												
30	randomised trials	not serious [c]	not serious	not serious	not serious	none	89/23196 (0.4%)	98/16728 (0.6%)	**RR 0.56** (0.39 to 0.79)	**3 fewer per 1,000** (from 4 fewer to 1 fewer) [h]	⊕⊕⊕⊕ HIGH	CRITICAL
								0.0% [g]		**0 fewer per 1,000** (from 0 fewer to 0 fewer)		

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DOACs	LMWH	Relative (95% CI)	Absolute (95% CI)		
Major bleeding (follow up: range 10 days to 35 days)												
32	randomised trials	not serious	not serious [i]	not serious	serious [b]	none	280/27464 (1.0%)	143/18918 (0.8%) 1.0% [j]	**RR 1.03** (0.79 to 1.35)	**0 fewer per 1,000** (from 2 fewer to 3 more) **0 fewer per 1,000** (from 2 fewer to 4 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Reoperation (follow up: range 10 days to 35 days)												
15	randomised trials	not serious	not serious	not serious	serious [b]	none	32/18919 (0.2%)	13/14641 (0.1%)	**RR 1.43** (0.75 to 2.71)	**0 fewer per 1,000** (from 0 fewer to 2 more)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. A sensitivity analysis excluding dose-finding studies was conducted and did not significantly change results in terms of point estimates or confidence intervals. Mortality: 0.94 [0.53, 1.66] I2=0% vs 0.79 [0.40, 1.57] I2=0%; Non Fatal Pulmonary embolism: 0.74 [0.50, 1.10] I2=0% vs 0.91 [0.43, 1.94] I2=35%; Symptomatic DVT: 0.56 [0.39, 0.79] I2 7% vs 0.50 [0.31, 0.81] I2=0%; Major bleeding: 1.03 [0.79, 1.35] I2 21% vs 1.11 [0.80, 1.52] I2=5%.

b. For decision making the certainty range around the effect estimates was felt to cross decision thresholds.

c. There was a considerable proportion of missing outcome data. We conducted a sensitivity analysis assuming that the risk of participants randomized but not counted in the intervention group was 3 times the risk of participants randomized and counted on the analysis. Also we assumed that the risk of participants randomized but not counted in the control group was the same that the risk of participants randomized and counted. Such analysis did not appreciably change the results.

d. The symptomatic PE population event rate of 0.56% was based on data from two retrospective cohort analyses of administrative records of 265,382 patients undergoing total hip or total knee arthroplasty in England and Wales (Jameson 2011, Jameson 2012).

e. The symptomatic proximal DVT rate of 0.588% was derived from data from two retrospective cohort analyses of administrative records of 265,382 patients undergoing total hip or total knee arthroplasty in England and Wales (Jameson 2011, Jameson 2012). The rate was calculated applying the assumption that 75% of all symptomatic DVTs (0.785%) are symptomatic proximal DVTs of moderate severity and considered a critical outcome.

f. The absolute risk difference is based on the study event rate of any symptomatic DVT (5.0%), which consisted of the surrogate composite outcome of any symptomatic proximal or distal DVT. Applying the assumption that only 75% of any symptomatic DVTs are proximal, the calculated absolute risk difference would be 2 fewer per 1,000 (from 3 fewer to fewer) based on an event rate of 0.45%.

g. The symptomatic distal DVT rate of 0.049% was derived from data from two retrospective cohort analyses of administrative records of 265,382 patients undergoing total hip or total knee arthroplasty in England and Wales (Jameson 2011, Jameson 2012). The rate was calculated applying the assumption that 25% of all symptomatic DVTs (0.785%) are symptomatic distal DVTs, of which 25% are assumed to be severe DVTs and considered a critical outcome.

h. The absolute risk difference is based on the study event rate of any symptomatic DVT (0.6%), which consisted of the surrogate composite outcome of any symptomatic proximal or distal DVT. Applying the assumption that only 25% of any symptomatic DVTs are distal, of which 25% are assumed to be severe DVTs and considered a critical outcome, the calculated absolute risk difference would be 0 fewer per 1,000 (from 0 fewer to 0 fewer) based on an event rate of 0.0375%.

i. Some heterogeneity detected (I2=21%), but we did not downgrade.

j. Gerken (2010) reports major bleeding rates of 1% for LMWH.

Table 4: Summary of included guidelines and related systematic review.

Author, date	Population	Interventions	Outcomes	Appraisal and comments
ASH 2018 guidelines on VTE prophylaxis for medically ill hospitalised patients, Holger J. Schunemann	3 RCTs Approximately 10 000 participants	Intervention (DOAC) rivaroxaban, apixaban and betrixaban Standard course inpatient treatment of 6 to 14 days of the LMWH enoxaparin with an extended treatment of 30 to 42 days of the DOAC	<u>VTE related mortality:</u> RR, 0.64; (95% CI, 0.21-1.98); risk difference, 0 fewer deaths per 1000; (95% CI, 1 fewer to 1 more per 1000); high certainty evidence <u>DVT</u> Symptomatic DVT: RR, 1.03; (95% CI, 0.34-3.08); risk difference, 0 fewer per 1000; (95% CI, 1 fewer to 2 more per 1000); moderate certainty evidence <u>PE</u> Nonfatal PE: RR, 1.01; (95% CI, 0.29-3.53); risk difference, 0 fewer per 1000; (95% CI, 1 fewer to 3 more per 1000); moderate certainty evidence <u>Major bleeding</u> RR, 1.70; (95% CI, 1.02-2.82); risk difference, 1 more per 1000; (95% CI, 0 or 4 more major bleeds); high certainty evidence	Appraisal: AGREE II – 6/7 The points were lost in stakeholder involvement and rigour development. The inclusion criteria was not stated in methods and was stated that it was published in a subsequent article. Recommendation: In acutely ill hospitalised medical patients, the ASH guideline panel recommends using LMWH over DOACs as VTE prophylaxis (strong recommendation, moderate certainty in the evidence of effects).
ASH 2019 guidelines on VTE prophylaxis for surgical hospitalised patients	38 RCTs Approximately 24 000 participants	DOACs (rivaroxaban, apixaban, dabigatran, darexaban, edoxaban and other (including betrixaban) Standard dosing of rivaroxaban: 10mg orally daily. Standard dosing of enoxaparin 40mg subcutaneously daily. Duration of treatment was variable and between 10 and 35 days	<u>Mortality:</u> RR 0.94 (95% CI 0.53 to 1.66); risk difference 0 fewer deaths (1 fewer to 1 more) per 1000 patients; moderate certainty evidence. <u>Deep Vein Thrombosis:</u> RR 0.56 (95% CI 0.39 to 0.79); risk difference 3 fewer per 1000 patients (4 fewer to 1 fewer); moderate certainty evidence. <u>Pulmonary Embolism</u> RR 0.74 (95% CI 0.50 to 1.10); risk difference 1 fewer (3 fewer to 1 more) per 1000 patients; high certainty evidence. Major bleeding: RR 1.03 (95% CI 0.79 to 1.35); risk difference 0 fewer (2 fewer to 3 more) per 1000 patients; moderate certainty evidence. <u>Reoperation</u> RR 1.43 (95% CI 0.75 to 2.71), risk difference 0 fewer (0 fewer to 2 more) per 1000 patients; moderate certainty evidence.	Appraisal: AGREE II – 6/7 The points were lost in stakeholder involvement and rigor of development. Recommendation: In patients undergoing total hip or knee arthroplasty in which anticoagulants are used, the ASH guideline panel suggests using DOACs over LMWH (conditional recommendation based on moderate certainty in the evidence of effects)

Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☒ Low ☐ Very low ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Medically ill, hospitalised patients: VTE outcomes (DVT and PE) were assessed as moderate certainty evidence, downgraded for serious imprecision. The outcome of mortality was assessed as high certainty. Overall, an assessment of moderate certainty was made. Surgical patients undergoing total hip or knee arthroplasty: Mortality and DVT outcomes were assessed as moderate certainty evidence, downgraded for serious imprecision. The outcome of pulmonary embolism was assessed as high certainty evidence. Overall, an assessment of moderate certainty was made.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☐ Small ☐ None ☒	Medically ill, hospitalised patients: There was no difference in mortality and similar risk of VTE outcomes with DOAC compared to LMWH use. • Mortality: RR, 0.64 (95% CI 0.21 to 1.98) • DVT: RR 1.03; (95% CI 0.34 to 3.08) • PE: RR 1.01 (95% CI 0.29 to 3.53) Surgical patients undergoing total hip or knee arthroplasty: There was a similar risk in mortality, no difference in risk of PE and decreased risk of DVT with DOAC compared to LMWH use. • Mortality: RR 0.94 (95% CI 0.53 to 1.66) • DVT: RR 0.56 (95% CI 0.39 to 0.79) • PE: RR 0.74 (95% CI 0.50 to 1.10)
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☒ Low ☐ Very low ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Medically ill, hospitalised patients: The outcome of major bleeding was assessed as high certainty evidence. Surgical patients undergoing total hip or knee arthroplasty: The outcome of major bleeding was assessed as moderate certainty evidence, downgraded for serious imprecision. The outcome of reoperation was assessed as moderate certainty evidence.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge ☐ Moderate ☐ Small ☒ None ☐	Medically ill, hospitalised patients: There was a trivial increase in risk of major bleeding with use of DOACs compared with LMWH • Major bleeding: RR 1.70 ((95% CI 1.02 to 2.82); 4 vs 2 major bleeds per 1000 patients = 2 more per 1000 with DOACs (0 more to 4 more); number needed to harm = 500 (95% CI 250 to ∞) Surgical patients undergoing total hip or knee arthroplasty: There was a similar risk of major bleeding and no difference in the risk of reoperation with use of DOACs compared with LMWH. • Major bleeding: RR 1.03 (95% CI 0.79 to 1.35) • Reoperation: RR 1.43 (95% CI 0.75 to 2.71) Overall there was a small increase in risk of harmful outcomes.

<table>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable harms?
Favours intervention [ ] Favours control [ ] Intervention = Control [X]</td><td>The intervention is non-inferior to control in terms of risk of VTE and mortality in both medically ill, hospitalised adults and surgical patients undergoing total hip or knee arthroplasty. There is no difference in risk of major bleeding or reoperation in surgical patients undergoing total hip or knee arthroplasty. The increase in risk of major bleeding in medically ill, hospitalised adults, is trivial and may be offset by cost-saving associated with use of the intervention.</td></tr>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available: n/a</td><td>This is a therapeutic multiple medicine review.</td></tr>
<tr><td>FEASABILITY</td><td>Is implementation of this recommendation feasible?
Yes [X] No [ ] Uncertain [ ]</td><td></td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive [ ] Less intensive [X] Uncertain [ ]

Significant savings to be made in switching from enoxaparin (current standard of care) to rivaroxaban for the prevention of VTE (See Appendix 2 for further detail).</td><td>Price of medicines/ daily dose
*The cost analysis in appendix 2 shows significant cost-saving when using rivaroxaban. Other DOACs are currently more expensive than rivaroxaban and formal cost analysis has not been performed.
<table><tr><th colspan="3">VTE prophylaxis</th></tr><tr><th>Drug</th><th>Price/unit</th><th>Cost per day per patient</th></tr><tr><td>Enoxaparin 40mg OD*</td><td>54.99</td><td>54.99</td></tr><tr><td>Rivaroxaban 10mg OD*</td><td>14.66</td><td>14.66</td></tr><tr><td>Apixaban 2.5mg BD**</td><td>14.75</td><td>29.49</td></tr><tr><td colspan="3">*MHPL – 1 Sep 2023
**SEP database – 14 Aug 2023</td></tr></table></td></tr>
<tr><td>VALUES, PREFERENCES, ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?
Minor [X] Major [ ] Uncertain [ ]

Is the option acceptable to key stakeholders?
Yes [ ] No [ ] Uncertain [X]</td><td>No local survey evidence could be sourced. Evidence from North America and Europe suggests that patients prefer oral prophylaxis over injection and were most concerned about the risk of pulmonary embolism.[12]</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?
Yes [X] No [ ] Uncertain [ ]</td><td>Massive cost-savings of choosing the intervention would impact budget allocation and allow for spending elsewhere to improve health equity.</td></tr>
</table>

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial (v5.0)	18 November 2021	RVR, VPL, TK, NT, MB, TL	DOACs not be used for the prevention of VTE, as there is no clear evidence of superior efficacy compared to LMWH, with an increased signal of harms.
V6.0	26 Sep 2023	GT, MB	Recommendation revised in view of the reduction in price of rivaroxaban and the revised comparative costs and changed in favour of using DOACs over LMWH.

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Appendix 1: Search strategy

Database: **CENTRAL (Issue 9 OF 12, September 2021)**
Date: **30 September 2021**

ID	Search	Hits
#1	[mh "venous thrombosis"] or phlebothrombos*:ti,ab or ("deep vein" next thrombos*):ti,ab or DVT:ti,ab, (Word variations have been searched)	6373
#2	[mh "pulmonary embolism"] or (pulmonary next embolism*):ti,ab or (pulmonary next thrombo*):ti,ab or PE:ti,ab (Word variations have been searched)	7591
#3	[mh "venous thromboembolism"] or (venous next thrombo*):ti,ab or VTE:ti,ab (Word variations have been searched)	6879
#4	#1 or #2 or #3	15555
#5	(oral next anticoagulant*):ti,ab (Word variations have been searched)	2003
#6	[mh dabigatran] or dabigatran:ti,ab'kw or pradaxa:ti,ab,kw or "BIBR 1048":ti,ab,kw (Word variations have been searched)	7591
#7	[mh rivaroxaban] or rivaroxaban:ti,ab,kw or xarelto:ti,ab,kw or "BAY 59 7939":ti,ab,kw or "BAY 597939":ti,ab,kw (Word variations have been searched)	1884
#8	apixaban:ti,ab,kw or eliquis:ti,ab,kw or "BMS 562247":ti,ab,kw or BMS562247:ti,ab,kw (Word variations have been searched)	1027
#9	#5 or #6 or #7 or #8	11019
#10	MeSH descriptor: [Heparin, Low-Molecular-Weight] explode all trees	2026
#11	[mh heparin] or heparin*:ti,ab,kw or liquaemin:ti,ab,kw or UFH:ti,ab,kw or LMW:ti,ab,kw or LMWH:ti,ab,kw or LMWHS:ti,ab,kw or "low-molecular-weight":ti,ab,kw or dalteparin:ti,ab,kw or enoxaparin:ti,ab,kw or nadroparin:ti,ab,kw or tinzaparin:ti,ab,kw or certoparin:ti,ab,kw or parnaparin:ti,ab,kw or ("vitamin K" next antagonist*):ti,ab,kw	15661
#12	#10 or #11	15661
#13	#4 and #9 and #12	804
#14	#4 and #9 and #12 with Publication Year from 2019 to 2021, in Trials	209

Database: **PubMed**
Date: **30 September 2021**

Search	Query	Results
#14	Search: #11 AND #12 Filters: from 2019/1/1 - 2021/9/30 Sort by: Most Recent	553
#13	Search: #11 AND #12 Sort by: Most Recent	2,081
#12	Search: (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals[mh] NOT humans[mh]) Sort by: Most Recent	4,533,027
#11	Search: #4 AND #9 AND #10 Sort by: Most Recent	3,169
#10	Search: heparin[mh] OR heparin*[tiab] OR heparinic acid[tiab] OR liquaemin[tiab] OR UFH[tiab] OR heparin, low-molecular-weight[mh] OR LMW [tiab] OR LMWH[tiab] OR LMWHS[tiab] OR low-molecular-weight[tiab] OR dalteparin[tiab] OR enoxaparin[tiab] OR nadroparin[tiab] OR tinzaparin[tiab] OR certoparin[tiab] OR parnaparin[tiab] OR vitamin K antagonist*[tiab] Sort by: Most Recent	151,273
#9	Search: #5 OR #6 OR #7 OR #8 Sort by: Most Recent	22,536
#8	Search: apixaban[nm] OR apixaban[tiab] OR eliquis[tiab] OR BMS 562247[tiab] OR BMS562247[tiab] Sort by: Most Recent	4,472
#7	Search: rivaroxaban[mh] OR rivaroxaban[tiab] OR xarelto[tiab] OR BAY 59 7939[tiab] OR BAY 597939[tiab] Sort by: Most Recent	6,858
#6	Search: dabigatran[mh] OR dabigatran[tiab] OR pradaxa[tiab] OR BIBR 1048[tiab] Sort by: Most Recent	5,993
#5	Search: "oral anticoagulant"[tiab] OR "oral anticoagulants"[tiab] Sort by: Most Recent	16,347
#4	Search: #1 OR #2 OR #3 Sort by: Most Recent	172,173
#3	Search: Venous thromboembolism[mh] OR venous thrombo*[tiab] OR VTE[tiab] Sort by: Most Recent	55,557
#2	Search: Pulmonary embolism[mh] OR pulmonary embolism*[tiab] OR pulmonary thrombo*[tiab] OR PE[tiab] Sort by: Most Recent	94,223
#1	Search: Venous thrombosis[mh] OR phlebothrombos*[tiab] OR deep vein thrombos*[tiab] OR DVT[tiab] Sort by: Most Recent	68,272

Appendix 2: BIA Analysis

National Essential Medicines List
Budget impact analysis
Adult Hospital Level
Component: BBFO

Date: 16 March 2023
Medication: Rivaroxaban
Indication: Prophylaxis of venous thromboembolic disease in hospitalised adult patients

1. INTRODUCTION

In January 2023, rivaroxaban was approved on a limited tender due to supply constraints with warfarin. Effective May 2023, rivaroxaban will be available in State on a limited tender as a non-EML medicine at a 52% discount to the SEP[1]. The formulations and approved prices are included in Table 1 below.

Table 1: Formulation and prices of rivaroxaban approved on limited tender[2]

Formulation	Pack size	Tender Price (May 2023)	Price/unit
Rivaroxaban; 10mg; Tablet	30 tablets	R439.66	R14.66
Rivaroxaban; 15mg; Tablet	42 tablets	R615.52	R14.66
Rivaroxaban; 20mg; Tablet	28 tablets	R410.35	R14.66

At these tender prices, the cost per dose of rivaroxaban is considerably less than enoxaparin 40mg (R53.61 per dose[3]), which is on tender for a number of indications, including, for the prevention of venous thromboembolic disease as medical and surgical prophylaxis in adult hospitalised patients. A budget impact analysis has been conducted to determine whether the current recommendation for the use of enoxaparin for the prevention of venous thromboembolic disease in hospitalised adult patients should be retained or whether rivaroxaban should be considered as an alternative.

Note:

1. The use of rivaroxaban for the treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and prevention of recurrent venous thromboembolic events (VTE) as well as for the prevention of stroke in atrial fibrillation (AF) have been addressed separately with warfarin as the current standard of care.
2. Evidence [4, 5] suggests that aspirin may be as effective as anticoagulants for the prevention of venous thromboembolism in moderate risk patients post orthopaedic surgery. This applies to prophylaxis of VTE in patients post total knee arthroplasty (TKA) and total hip arthroplasty (THA), as well as patients with trauma-related operative extremity fractures or any pelvic or acetabular fracture (operative or non-operative). Evidence for VTE prophylaxis with aspirin post TKA or THA is of variable quality and difficult to synthesize owing to variability in dosing, duration of therapy, adjunct mechanical measures for VTE prophylaxis and risk stratification to determine which methods of prophylaxis should be utilised. In this patient demographic (post TKA or THA), there is a proportion of patients in whom VTE prophylaxis with aspirin may be non-inferior. A more robust recommendation could be made for low to moderate risk

[1] Database of Medicine Prices Dec 2022. Ixarola 10mg unit price =R30.60 effective 18 Feb 2022.

[2] HP09 contract circular 7 Feb 2023 effective from May 2023

[3] MHPL Mar 2023

[4] Mistry DA, Chandratreya A, Lee PYF. A Systematic Review on the Use of Aspirin in the Prevention of Deep Vein Thrombosis in Major Elective Lower Limb Orthopedic Surgery: An Update from the Past 3 Years. Surg J (N Y). 2017 Dec 29;3(4):e191-e196. doi: 10.1055/s-0037-1615817. PMID: 29302621; PMCID: PMC5747531.

[5] Major Extremity Trauma Research Consortium (METRC); O'Toole RV, Stein DM, O'Hara NN, Frey KP, Taylor TJ, Scharfstein DO, Carlini AR, Sudini K, Degani Y, Slobogean GP, Haut ER, Obremskey W, Firoozabadi R, Bosse MJ, Goldhaber SZ, Marvel D, Castillo RC. Aspirin or Low-Molecular-Weight Heparin for Thromboprophylaxis after a Fracture. N Engl J Med. 2023 Jan 19;388(3):203-213. doi: 10.1056/NEJMoa2205973. PMID: 36652352.

patients with trauma-related fractures, although not all patients may receive prophylaxis and the duration of prophylaxis is invariably short (3 days). In these patient populations in which patients are at high risk of VTE or where aspirin is not appropriate, rivaroxaban may be considered.

2. LICENSED INDICATIONS

The SAHPRA approved indications for rivaroxaban and enoxaparin for prevention of thromboembolic disease are tabulated below. Comparison to U.S. and UK registered indications also included.

Table 2: Comparative registered indications for enoxaparin and rivaroxaban

MEDICINE	INDICATION	REGULATORY APPROVAL			TREATMENT COST
		S.A.	UK	US	
Rivaroxaban	Prophylaxis of venous thromboembolism after knee or hip surgery: 10 mg once daily, within 6–10 hours after surgery provided that haemostasis has been established. Treatment should be continued for 2 weeks after major knee surgery and for 5 weeks after hip surgery.	Y	Y	Y	Knee R205.24 Hip R513.10
Rivaroxaban	Venous thromboembolism (VTE) prophylaxis in acutely ill hospitalised patients at increased risk for thromboembolic complications but not at high risk of bleeding, 10 mg once daily, can be started during the hospital stay and continued for 31 to 39 days.	N	N	Y	*Variable based on length of stay*
Enoxaparin	Prevention of venous thrombosis after orthopaedic surgery: SC, 40 mg once daily, initiated 12 hours pre-operatively and continued for as long as risk persists (generally for 7–10 days; hip replacement, 3 weeks	Y	Y	Y	Orthopaedic R536.10 Hip R1125.81
Enoxaparin	Prevention of venous thrombosis in medical patients: SC, 40 mg once daily continued until fully ambulatory; minimum duration of therapy, 6 days.	Y	Y	Y	*Variable based on length of stay*

3. SAFETY AND EFFICACY

SURGICAL PROPHYLAXIS

The RECORD 1, 2, 3 and 4 studies were considered by NICE in their consideration for the use of rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults[6]. NICE concluded that rivaroxaban was at least as effective as enoxaparin in preventing VTE, noting an increase in the relative risk of major bleeding. The incidence of treatment-emergent major bleeding was the main safety endpoint in the RECORD trials. The rates of major bleeding as reported for the four studies for rivaroxaban versus enoxaparin is as follows: RECORD 1: 0.3% vs 0.1%, p = 0.178; RECORD 2: 0.1% vs 0.1%, p = 0.98; RECORD 3: 0.6% vs 0.5%, p = 0.77; and RECORD 4: 0.7% vs 0.3%, p = 0.11. An overview of the four studies assessed is included below:

[6] NICE TAG (TA170) rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults (April 2009)

3.1 SURGICAL PROPHYLAXIS – HIP

RECORD 1[7] (n=4541) was a multicentre, prospective, double-blind, parallel-group design RCT comparing rivaroxaban with enoxaparin for the prevention of VTE after total hip replacement surgery. Rivaroxaban was administered at a dosage of 10 mg once daily for 35 days starting on the day of surgery. Enoxaparin was administered at a dosage of 40 mg starting 1 day before surgery and for 35 days thereafter. A composite primary endpoint, defined as the composite of deep-vein thrombosis (either symptomatic or detected by bilateral venography if the patient was asymptomatic), nonfatal pulmonary embolism, or death from any cause at 36 days (range, 30 to 42), between rivaroxaban and enoxaparin based on a 'modified' intention to treat (MITT) analysis was reported. The primary endpoint occurred in 1.1% of the rivaroxaban group compared with 3.7% of the enoxaparin group; relative risk reduction (RRR) was 70% (95% confidence interval [CI] 49 to 82, p < 0.001).

RECORD 2[8] (n=2509) was a multicentre, prospective, double-blind, parallel-group design comparing 35 days of prophylaxis with rivaroxaban 10mg OD with 15 days of enoxaparin 40mg OD in patients undergoing total hip surgery. A statistically significant difference in the incidence of the composite primary endpoint (defined as the composite of deep-vein thrombosis (symptomatic or asymptomatic detected by mandatory, bilateral venography), non-fatal pulmonary embolism, and all-cause mortality up to day 30–42), between rivaroxaban and enoxaparin in the MITT analysis was reported; 2.0% in the rivaroxaban group compared with 9.3% in the enoxaparin group (RRR 79%, 95% CI 65 to 87).

3.2 SURGICAL PROPHYLAXIS – KNEE

RECORD 3[9] (n = 2531) was a multicentre, prospective, double-blind, parallel-group design RCTs comparing prophylaxis of rivaroxaban (10mg OD for 10-14 days) with enoxaparin (40mg OD a day before surgery and for 10-14 days thereafter) in patients undergoing total knee replacement surgery. The MITT was reported as a statistically significant difference in the incidence of the composite primary endpoint which was the composite of any deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE) and all-cause mortality: 9.6% in the rivaroxaban group compared with 18.9% in the enoxaparin group (RRR 49%, 95% CI 35 to 61). Major VTE occurred in 9 (1.0%) patients receiving rivaroxaban compared with 24 (2.6%) patients receiving enoxaparin (RRR 62%, 95% CI 18 to 82; p = 0.02).

RECORD 4[10] (n = 3148) was a multicentre, prospective, double-blind, parallel-group design RCTs comparing enoxaparin 30 mg twice daily starting 1 day before surgery and continuing for 10–14 days thereafter. The composite primary outcome (defined as the composite of any deep-vein thrombosis, non-fatal pulmonary embolism, or death from any cause up to day 17 after surgery), occurred in 6.9% and 10.1% of the rivaroxaban and enoxaparin groups, respectively (p < 0.012), with a lower incidence of major VTE events in the rivaroxaban arm.

SAFETY

The incidence of treatment-emergent bleeding was the main safety endpoint in the RECORD studies which was reported for rivaroxaban and enoxaparin respectively, as follows: RECORD 1: 0.3% vs 0.1%, p = 0.178; RECORD 2: 0.1% vs 0.1%, p = 0.98; RECORD 3: 0.6% vs 0.5%, p = 0.77; and RECORD 4: 0.7% vs 0.3%, p = 0.11.

[7] Eriksson BI, et al; RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med. 2008 Jun 26;358(26):2765-75. doi: 10.1056/NEJMoa0800374. PMID: 18579811.

[8] Ajay K Kakkar, et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial, The Lancet,Volume 372, Issue 9632, 2008, Pages 31-39.

[9] Lassen M, Ageno W, Bandel T, et al. RIVAROXABAN FOR THROMBOPROPHYLAXIS AFTER TOTAL KNEE REPLACEMENT: THE RECORD3 TRIAL. Orthop Procs. 2010;92-B(SUPP_II):289-290. doi:10.1302/0301-620X.92BSUPP_II.0920289d

[10] Turpie AG, et al. RECORD4 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet. 2009 May 16;373(9676):1673-80. doi: 10.1016/S0140-6736(09)60734-0. Epub 2009 May 4. Erratum in: Lancet. 2022 Dec 10;400(10368):2048. PMID: 19411100.

RECENT UPDATES ON RECORD 4:

Recent revelations on the RECORD 4 study[11] indicate that the study was excluded by the FDA as unreliable and that the FDA registration granted in 2011 was based on the results of the RECORD 1, 2 and 3 studies only, which were deemed reliable.

A correction statement was subsequently issued by the RECORD4 Steering Committee and published in the Lancet in Dec 2022[12]. The Committee advised that previous FDA reports from the RECORD 4 study revealed that 1227 of 3148 patients enrolled in RECORD4 might have been randomised postoperatively rather than preoperatively, as stated in the protocol. The FDA concluded that it would need to exclude 652 of the 3148 patients. Furthermore, the Steering Committee also learned that adverse events and serious adverse events had been under-reported at the 9·9% of sites audited for RECORD4 and recommended that the safety data reported in Table 4 of the original paper are inaccurate and should be disregarded. The FDA did not report any concerns regarding the primary efficacy and safety outcomes. The steering committee indicated that they were only made aware of the discrepancies in October 2022.

Note: the dose of enoxaparin used in RECORD 4 was 30mg BD which does not reflect local standard of care.

A more recently published systematic review (SR)[13] comparing the efficacy and safety of rivaroxaban and enoxaparin for thromboprophylaxis in orthopaedic surgery included five RCTS. This SR excluded the following three studies for reasons as specified:

- RECORD 2: Patients were randomised to receive oral rivaroxaban 10 mg once daily for 31–39 days (with placebo injection for 10–14 days; or enoxaparin 40 mg once daily subcutaneously for 10–14 days (with placebo tablet for 31–39 days. This study was excluded as the durations of the intervention drug and comparator drug were not the same as those of the other studies included in the SR (rivaroxaban was given for 39 days)
- RECORD 4: Patients were randomised to receive either oral rivaroxaban 10 mg once daily, beginning 6-8 h after surgery, or subcutaneous enoxaparin 30 mg every 12 h, starting 12-24 h after surgery. This study was excluded as the dose of enoxaparin was 30mg).
- RCT by Kim et al[14]: A prospective study in which patients with an age < 60 years were randomly assigned to three groups (rivaroxaban, enoxaparin, and placebo) and the patients with an age ≥ 60 years were assigned to two groups (rivaroxaban and enoxaparin). All drug regimens started at 12 hours postoperatively and continued for two weeks after surgery. This study was also excluded as the two age groups (<60 and >/=60 years old) were given different regimens.

Authors of the SR concluded that rivaroxaban was superior to enoxaparin as rivaroxaban significantly reduced the incidence of VTE and all-cause mortality based on the obtained risk ratio of 0.38 (95% CI = 0.27–0.54 (Figure 1 below). An AMSTAR assessment was completed to assess the quality of this SR, which was assessed to be of moderate quality.

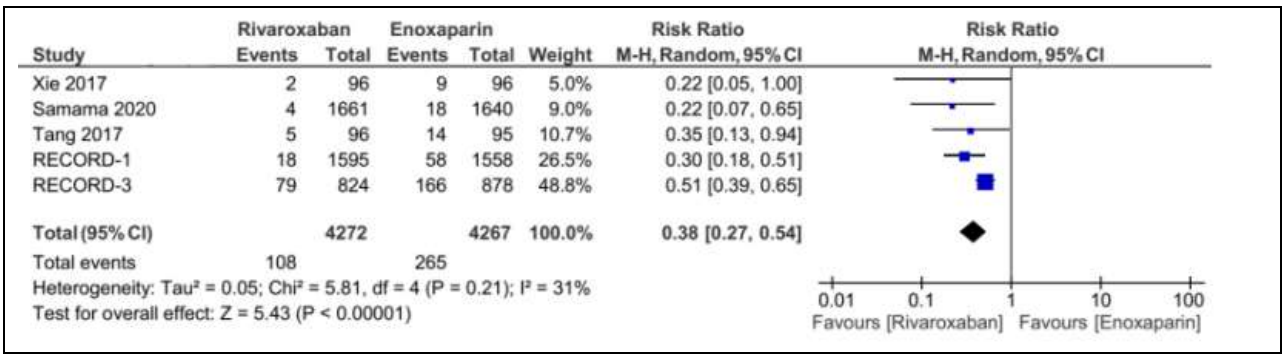
[11] RECORD4 Trial of Rivaroxaban, Published in 2009, Still Turning Heads | tctmd.com accessed 8 Mar 2023

[12] Turpie AA. Revisiting Record 4. The Lancet. Vol 400 December 10, 2022

[13] Rinaldi I, Amin IF, Shufiyani YM, Dewantara IR, Edina BC, Winston K, Nurrobi YAS. Comparison of the Efficacy and Safety of Rivaroxaban and Enoxaparin as Thromboprophylaxis Agents for Orthopedic Surgery-Systematic Review and Meta-Analysis. J Clin Med. 2022 Jul 14;11(14):4070. doi: 10.3390/jcm11144070. PMID: 35887834; PMCID: PMC9315734.

[14] Kim, S.M.; et al. Effect of oral factor Xa inhibitor and low-molecular-weight heparin on surgical complications following total hip arthroplasty. Thromb. Haemost. 2016, 115, 600–607. Available online: https://pubmed.ncbi.nlm.nih. gov/26790579/

Figure 1: Incidence of any VTE and all-cause death



In terms of safety, the authors investigated two factors for clinically relevant bleeding: (1) all bleeding (major and minor hemorrhage), and (2) major bleeding. Major bleeding was defined as bleeding that is potentially lethal to the patient and results in a reduction of Hemoglobin (Hb) by greater or equal than 2 g/dL based on laboratory evidence. The authors concluded that the incidence of any clinically relevant bleeding was not different between rivaroxaban and enoxaparin with a reported risk ratio of 1.07 (95% CI = 0.9–1.27 (Figure 2), including a non-significant difference in major bleeding. (Figure 3).

Figure 2: Incidence of any clinically relevant bleeding (major bleeding and any other clinically relevant bleeding)

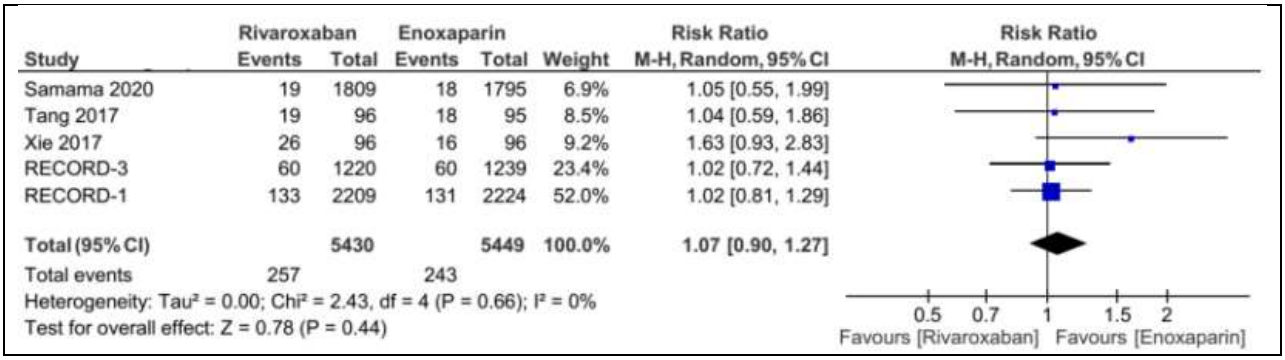
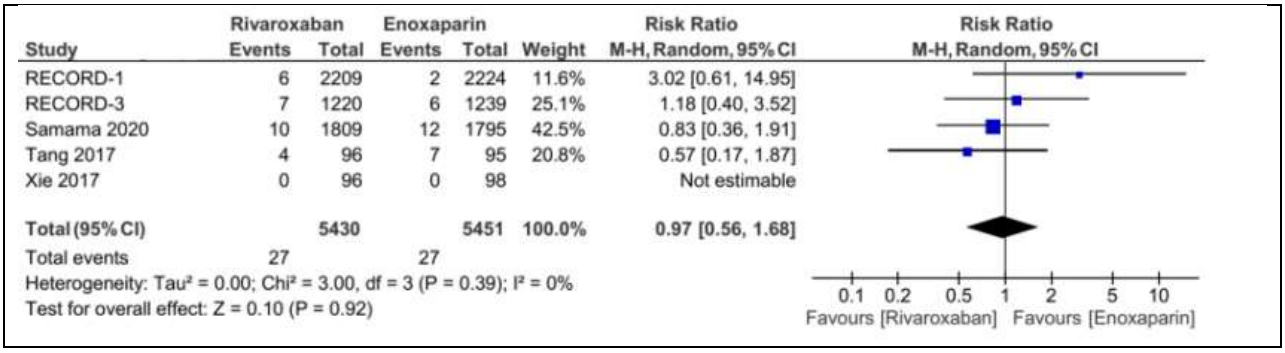


Figure 3: Incidence of major bleeding



3.3 MEDICAL PROPHYLAXIS

Rivaroxaban was approved by the FDA for the prevention of venous thromboembolism (VTE), or blood clots, in hospitalised acutely ill medical patients at risk for thromboembolic complications who are not at high risk of bleeding, in

October 2019. The two pivotal RCTS (the MAGELLAN 2013 and MARINER 2018 studies) included over 20000 acutely ill hospitalised patients.

MAGELLAN (n=8101)[15]: a double-blind RCT in which patients hospitalised for an acute medical illness received either enoxaparin SC, 40 mg once daily, for 10±4 days and oral placebo for 35±4 days or SC placebo for 10±4 days and oral rivaroxaban, 10 mg once daily, for 35±4 days. Primary efficacy outcomes were the composite of asymptomatic proximal or symptomatic venous thromboembolism up to day 10 (non-inferiority test) and up to day 35 (superiority test). The primary efficacy outcome event occurred in 78 of 2938 patients (2.7%) receiving rivaroxaban and 82 of 2993 patients (2.7%) receiving enoxaparin at day 10 (relative risk with rivaroxaban, 0.97; 95% confidence interval [CI], 0.71 to 1.31; P=0.003 for non-inferiority) and in 131 of 2967 patients (4.4%) who received rivaroxaban and 175 of 3057 patients (5.7%) who received enoxaparin followed by placebo at day 35 (relative risk, 0.77; 95% CI, 0.62 to 0.96; P=0.02). The composite of major or clinically relevant non-major bleeding which was a key safety outcome was reported in 111 of 3997 patients (2.8%) in the rivaroxaban group and 49 of 4001 patients (1.2%) in the enoxaparin group at day 10 (relative risk, 2.3; 95% CI, 1.63 to 3.17; P<0.001). For the extended duration, clinically relevant bleeding occurred in 164 of 3997 patients (4.1%) in the group that received extended-duration rivaroxaban as compared with 67 of 4001 patients (1.7%) in the group that received enoxaparin followed by placebo (relative risk, 2.5; 95% CI, 1.85 to 3.25; P<0.001). The authors concluded that rivaroxaban was non-inferior to enoxaparin for standard duration prophylaxis (6-14 days). They also reported a reduced risk of venous thromboembolism with extended duration rivaroxaban (31-39 days). Rivaroxaban was, however, associated with a greater risk of bleeding.

A sub-group analyses of data from the MAGELLAN study identified 5 key factors associated with increased bleeding risk: active cancer, gastrointestinal ulcer, bronchiectasis/pulmonary cavitation, bleeding in the previous 3 months, or concomitant use of dual antiplatelet therapy.

Patients with these risk factors were not eligible for inclusion in the MARINER study conducted subsequently.

MARINER (n=12024)[16]: A double-blind RCT in which medically ill patients at increased risk of VTE (on the basis of a modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) score of 4 or higher (scores range from 0 to 10, with higher scores indicating a higher risk of venous thromboembolism) or a score of 2 or 3 plus a plasma d-dimer level of more than twice the upper limit of the normal range (defined according to local laboratory criteria), were given either once-daily rivaroxaban at a dose of 10 mg (with the dose adjusted for renal insufficiency) or placebo for 45 days at hospital discharge. The mean age of study participants was 67.8 years and, with women accounting for 44.5% of the population which was predominantly white (96.5%). For the primary efficacy outcome, which was a composite of symptomatic venous thromboembolism or death due to venous thromboembolism, outcomes were reported in 50 of 6007 patients (0.83%) who were given rivaroxaban and in 66 of 6012 patients (1.10%) who were given placebo (hazard ratio, 0.76; 95% confidence interval [CI], 0.52 to 1.09; P=0.14). The pre-specified secondary outcome of symptomatic nonfatal venous thromboembolism occurred in 0.18% of patients in the rivaroxaban group and 0.42% of patients in the placebo group (hazard ratio, 0.44; 95% CI, 0.22 to 0.89). Major bleeding occurred in 17 of 5982 patients (0.28%) in the rivaroxaban group and in 9 of 5980 patients (0.15%) in the placebo group (hazard ratio, 1.88; 95% CI, 0.84 to 4.23). Important to note though that patients with high risk factors for bleeding such as: active cancer, gastrointestinal ulcer, bronchiectasis/pulmonary cavitation, bleeding in the previous 3 months, or concomitant use of dual antiplatelet therapy, were excluded.

[15] Cohen AT et al. Rivaroxaban for Thromboprophylaxis in Acutely Ill Medical Patients. NEJM 7 feb 2013 p513-522.

[16] Spyropoulos AC et al. Rivaroxaban for Thromboprophylaxis after Hospitalization for Medical Illness. NEJM 20 Sep 2018.

3 BUDGET IMPACT

A budget impact assessment was conducted to assess the potential cost savings that could be made in switching from enoxaparin to rivaroxaban for the prevention of thromboembolic disease in hospitalised patients. Utilisation data for Clexane® 40mg for 2021 (Jan-Dec) and 2022 (Jan-Oct) across the provinces was used, and two scenarios are presented, based on an assumed switch rate of 30% and 70% respectively (note however, that rivaroxaban is not currently registered by SAHPRA for medical prophylaxis). Based on the new May 2023 tender prices, rivaroxaban would offer a cost saving of R38.95 for every dose of enoxaparin 40mg administered.

Table 3a: Projected savings with a 30% switch rate from enoxaparin 40mg to rivaroxaban 10mg

ACTUAL QUANTITIES ORDERED			ASSUMED SWITCH RATE 30% WITH RIVAROXABAN		
	ENOXAPARIN 40mg (R53.61 per dose)		RIVAROXABAN	ENOXAPARIN	Projected Saving - ZAR
Period	Pk size=10	Calculated Spend-ZAR			
Jan- Dec 2021	289 237	R 155 059 955.70	R 12 720 643.26	R 108 541 968.99	**R 33797343.45**
Jan-Oct 2022*	213 110	R 114 248 271.00	R 9 372 577.80	R 79 973 789.70	**R 24 901 903.50**

*Data for Nov and Dec not yet reported

Table 3b: Projected savings with a 70% switch rate from enoxaparin 40mg to rivaroxaban 10mg

ACTUAL QUANTITIES ORDERED			ASSUMED SWITCH RATE 70% WITH RIVAROXABAN		
	CLEXANE 40mg (R53.61 per dose)		RIVAROXBAN	CLEXANE	Projected Saving - ZAR
Period	Pk size=10	Calculated Spend-ZAR			
Jan- Dec 2021	289 237	R155 059 955.70	R29 681 500.94	R46 517 986.71	**R 78 860 468.05**
Jan-Oct 2022*	213 110	R114 248 271.00	R21 869 348.20	R34 274 481.30	**R 58 104 441.50**

*Data for Nov and Dec not yet reported

Based on the 2021 (Jan-Dec) utilisation of enoxaparin, the anticipated spend on enoxaparin at the price of R53.61 would be R155.1m and for 2022 (Jan-Oct) R114.2m (includes the COVID-related spend for thromboprophylaxis during 2021). Assuming a 30% switch rate to rivaroxaban, a cost saving of R33.8m would be achieved based on 2021 utilisation and R24.9m for 2022. Similarly, assuming a switch rate of 70% to rivaroxaban, the estimated cost saving would be R78.9m for 2021 and R58.1m for 2022 based on available utilisation data.

We acknowledge that a 100% switch rate will not be feasible as certain patient cohorts will still require enoxaparin. These cohorts include pregnant patients, paediatric patients and surgical patients other than orthopaedic patients undergoing hip or knee arthroplasty.

Note:

- The budget impact is based on medicine costs only and indirect costs related to administration (SC v oral), monitoring and management of adverse effects have not been included.

- The impact of any resultant competitive market dynamics has not been included e.g. any potential cost reduction with enoxaparin or the introduction of generic rivaroxaban, both of which would support further cost savings.
- There is emerging evidence of extended thromboprophylaxis in medically ill patients for up to 45 days following an acute hospitalisation [17], which has not been included in the budget impact analysis. Extended thromboprophylaxis is currently not included on the EML. We do however recognise the risk of scope creep particularly since rivaroxaban is an oral formulation and will be easier for patient self-administration compared to SC administration of enoxaparin. This potential scope creep could negatively impact the projected cost savings.
- Should rivaroxaban be included on the EML for the prophylaxis of thromboembolic disease in hospitalised adult patients there is a potential for scope creep with other indications e.g. atrial fibrillation where the cost effectiveness of rivaroxaban has not been demonstrated when compared to current standard of care.

4 RECOMMENDATION

Based on the approved tender price of R14.66 for rivaroxaban 10mg effective as of May 2023, we recommend a switch from enoxaparin 40mg to rivaroxaban 10mg for prophylaxis of thromboembolic disease in medically ill hospitalised adult patients and surgical, adult, patients undergoing hip or knee arthroplasty, as clinically appropriate.

Extended thromboprophylaxis post-discharge, is not supported in medically ill patients as evidence of safety with regard to bleeding risks has not been demonstrated in patients with additional risk factors for bleeding such as active cancer, gastrointestinal ulcer, bronchiectasis/pulmonary cavitation, bleeding in the previous 3 months, or concomitant use of dual antiplatelet therapy, which were all exclusions in the MARINER study. Thromboprophylaxis in total hip or total knee arthroplasty may however continue post discharge as duration of prophylaxis is recommended for a minimum of 14 days and up until 35 days post surgery.

Report prepared by: Prof M. Blockman and Ms Z.Adam

Conflicts of interest: MB and ZA have no conflicts of interests related to rivaroxaban.

[17] MacDougall K, Spyropoulos AC. New Paradigms of Extended Thromboprophylaxis in Medically Ill Patients. J Clin Med. 2020 Apr 2;9(4):1002. doi: 10.3390/jcm9041002. PMID: 32252423; PMCID: PMC7230788.