South African National Essential Medicine List
Adult Hospital Medication Review Process
Component: Blood and blood forming organs

MEDICINE REVIEW

1. Executive Summary

Date: July 2023
Medicine (INN): Aspirin
Medicine (ATC): B01AC06
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 patients with trauma-related operative or non-operative extremity fractures or trauma-related pelvic or acetabular fractures at risk of venous thromboembolism
Prevalence of condition: All hospitalised patients at risk with trauma-related operative extremity fractures or either operative or non-operative trauma-related pelvic or acetabular fractures
Prescriber Level: AH
Motivator/reviewer name(s): Prof Marc Blockman, Dr Gayle Tatz, Ms Zahiera Adam
PTC affiliation: WC PTC –Marc Blockman

Key findings

- A systematic review was conducted to evaluate the efficacy of aspirin compared with low-molecular weight heparin (LMWH) in adult patients requiring venous thromboembolism (VTE) prophylaxis after trauma-related fractures.
- We identified two relevant trials, Haac 2020 (ADAPT) and O'Toole 2023 (METRC) conducted in USA and Canada, n = 12,540. Both trials tested aspirin (81 mg twice daily) vs enoxaparin (30mg twice daily).
- Overall, aspirin is probably no different to enoxaparin for:
  - mortality — RR 1.07 (95% CI 0.71 to 1.59); risk difference (RD) 1 more death (2 fewer to 4 more) per 1000 people treated with aspirin vs enoxaparin
  - major bleeding — RR 0.96 (0.89 to 1.05); RD 6 fewer per 1000 people (16 fewer to 7 more) treated with aspirin vs enoxaparin, and
  - pulmonary emboli — RR 0.77 (0.30 to 1.94); RD 4 fewer events (11 fewer to 14 more) per 1000 people treated with aspirin vs enoxaparin (high certainty evidence).
- However, using aspirin compared to enoxaparin, likely results in a small increase in the risk of developing symptomatic deep vein thrombosis (DVT) RR 1.48 (1.16 to 1.89); RD 8 more per 1000 (3 more to 15 more).
- A large proportion of the screened participants in the two trials included in this review, were excluded at the treating clinician's discretion. In most cases, this was likely due to the excluded patients being at higher risk of VTE, although specific reasons were not provided. This data may therefore represent a lower risk population in which prophylaxis with aspirin may perform better.
- In the South African public sector, enoxaparin is the current recommended medicine for VTE prophylaxis in this patient population. It is costly and administered subcutaneously. Aspirin is extremely cheap, taken orally and is easily accessible in most facilities at every level of care across the country. Using aspirin rather than enoxaparin,

may lead to major cost-savings and improved access to outpatient VTE prophylaxis, which may reduce duration of hospital stay. There is however, the potential for increased cases of DVT

- Risk stratification may be useful in determining the patient population in whom VTE prophylaxis with aspirin would be a safe choice.

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 aspirin as prophylaxis in patients with operative trauma-related extremity fractures for all operative or non-operative hip and acetabular fractures. It must be noted that this recommendation is conditional as it applies only to patients with low to moderate risk of VTE. The studies included are representative of a low to moderate risk population and findings cannot therefore be extrapolated to patients at high risk of VTE. A recommended dose of 150mg of aspirin daily, initiated >12 hours post-operatively and continued for 14 days or until mobilisation is achieved should be given to low-moderate risk patients without contraindications to aspirin, and requiring thromboprophylaxis. In patients with non-operative pelvic and acetabular fractures, prophylaxis can be continued for up to 35 days. VTE risk can be determined by using the Caprini score or risk categories stipulated in the current Standard Treatment Guidelines as detailed for surgical patients.

Rationale: There is no difference in incidence of death, pulmonary embolism or major bleeding between VTE prophylaxis with aspirin compared with enoxaparin. In addition, the increased risk of DVT with use of aspirin is trivial and does not translate into increased risk of pulmonary embolus or death. The cost incurred by the additional cases of DVT are likely to be far-surpassed by the major cost savings of using aspirin over enoxaparin.

Level of Evidence: moderate
Review indicator: New data on the efficacy and/or safety

NEMLC RECOMMENDATION (MEETING OF 12 October 2023): NEMLC supported the recommendation pending the editorial amendments as discussed. The EML should include guidance on risk stratification and the STG recommendation for the use of aspirin for VTE prophylaxis should be aligned to the population as specified in the PICO.

Monitoring and evaluation considerations: A formal cost-analysis maybe performed to quantify the extent of the potential savings.

Research priorities

Prospero registration: na

Name of author(s)/motivator(s):
Gayle Tatz, Ntombifuthi Blose, Mashudu Mthethwa, Zahiera Adam, Sumayyah Ebrahim, Tamara Kredo, Marc Blockman

Author affiliation and conflict of interest details
Gayle Tatz (Clinical Pharmacology at the Groote Schuur Hospital, University of Cape Town); NB and MM (Health Systems Research Unit, South African Medical Research Council (SAMRC); TK (Health Systems Research Unit, SAMRC and Division of Clinical Pharmacology, Department of Medicine and Division of Epidemiology and Biostatistics, Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University; TK is co-director of the South African GRADE Network. ZA (Consultant for Right to Care), no conflicts to declare.

Acknowledgments:
TK, NB, MM and SE are partly supported by the Research, Evidence and Development Initiative (READ-It) project. READ-It (project number 300342-104) is funded by UK aid from the UK government; however, the views expressed do not necessarily reflect the UK government's official policies).
This review was supported by the SA GRADE Network, which is jointly led and managed by Centre for Evidence Based Health Care (CEBHC), Stellenbosch University and the Health Systems Research Unit, South African Medical Research Council.

INTRODUCTION

Deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively known as venous thromboembolism (VTE), are well-known and significant complications that can occur after major surgical procedures. Major surgical procedures are defined as interventions with higher-than-minimal risk, performed in the operating theatre, and requiring specialised training. In the past, before the routine use of effective preventive measures, VTE was a common cause of illness and death following major surgery, resulting in over 50,000 deaths annually in the United States alone (1). The importance of preventive measures to reduce the risk of VTE after major surgery has been acknowledged for many years, although even with the use of preventive measures, surgery still contributes to about 25% of VTE cases(2).

While most surgical procedures involve some risk of VTE, the level of risk varies among different types of surgeries and individual patients. Procedures such as hip and knee arthroplasty, invasive neurosurgical procedures, and major vascular surgeries carry the highest risk of postoperative VTE (3). Certain patient factors increase the risk of thrombosis such as a history of VTE, presence of malignancy and advancing age (4).

Scoring systems like the Caprini score have been developed and validated to assess the risk of postoperative VTE in individual patients undergoing specific surgical procedures, although this scoring system has been studied in many different circumstances including medical patients (4,5). Across board, a Caprini score of 7 or more is associated with a high risk of VTE. (Appendix 5) The South African Standard Treatment Guidelines, Hospital level, adults, 2019 edition, includes risk stratification criteria which may also be used to determine risk. (Appendix 7). Traditionally, postoperative VTE was primarily observed during hospital stays. However, with shorter hospital stays becoming more common, postoperative VTE now often occurs in the days to weeks following discharge from the hospital (4).

The current standard of care for venous thromboembolism (VTE) prophylaxis in patients undergoing surgery for hip or knee arthroplasty and for non-operative trauma-related pelvic and acetabular fractures is low molecular weight heparin (LMWH) e.g. enoxaparin. Recently, randomised controlled trials have suggested that other medications may be used as VTE prophylaxis with non-inferior efficacy and a similar safety profile. These medicines include aspirin, which has been used for multiple other indications for decades, and direct oral anticoagulants (DOACs) which are much newer (6, 7).

Aspirin is a much cheaper medication than any of the currently available DOACs and currently, both aspirin and DOACs (eg. rivaroxaban) are more affordable than enoxaparin. Replacing enoxaparin with aspirin for VTE prophylaxis for patients with operative trauma-related extremity fractures and for non-operative trauma-related pelvic and acetabular fractures, could result in significant cost-savings. The purpose of this review is to investigate the efficacy and safety of such an initiative.

RESEARCH QUESTION

What is the efficacy and safety of *aspirin* compared to *low molecular weight heparin* in adult patients requiring VTE prophylaxis for orthopaedic surgery?

METHODS

We searched guideline clearinghouses such as the National Institute for Health and Care Excellence (NICE), American College of Cardiology (ACC), Canadian Agency for Drugs and Technologies in Health, American Society of Hematology (ASH), Scottish Intercollegiate Guideline Network (SIGN), European Society of Cardiology, and the American College of Chest Physicians (ACCP) on the 15 May 2023 for eligible guidelines. Additionally, we systematically searched PubMed and the Cochrane Library on the 2 June 2023 for eligible systematic reviews and randomised controlled trials (RCTs), published from the year 2019 to June 2023, as guided by the 2019 ASH guideline. Search terms used are found in Appendix 1. Screening of records, and selection of articles was done independently and in duplicate by two reviewers (MM and NB) with conflict resolution by a third reviewer (SE). Data extraction was done by one reviewer (NB) and checked by a second reviewer (MM). The main characteristics of the included study and study outcomes are shown in Appendix 2 and 3.

Review Manager (RevMan) 5 software was used to perform the analyses. We reported risk ratios for dichotomous data with 95% confidence intervals (CI). GRADE was used to assess the overall confidence of the evidence considering various factors that may decrease our confidence in the trial finding including risk of bias, inconsistency, imprecision, publication bias and indirectness (9). Appendix 3 is a GRADE evidence profile for the comparison of aspirin compared to LMWH. GRADE summary of findings table for this comparison reported in results (Table 3).

Eligibility criteria for review

Table 1: PICO framework

Population	Adult patients requiring VTE prophylaxis for orthopaedic trauma Population: trauma-related operative extremity fracture (proximal to the metatarsals or carpals) OR trauma-related operative or non-operative pelvis or acetabular fracture
Intervention	Aspirin
Control	Low-molecular-weight heparin
Outcomes	1. Mortality 2. Pulmonary embolism 3. Deep vein thrombosis 4. Major bleeding
Study designs	Guidelines, then systematic review of trials and if not found, then clinical trials

RESULTS

Result of search for guidelines

No guidelines identified that were relevant to the population as described in our PICO.

Result of search for systematic reviews and trials

We searched for reviews on aspirin use for arthroplasty or fractures for convenience for a related review. Three hundred and twenty-four potentially eligible records were retrieved from PubMed and the Cochrane Library databases. Of those, three hundred and twenty-two were excluded and two records (Haac 2020 et al., and O'Toole 2022 et al.,) were included in the pooled analysis (Figure 2).

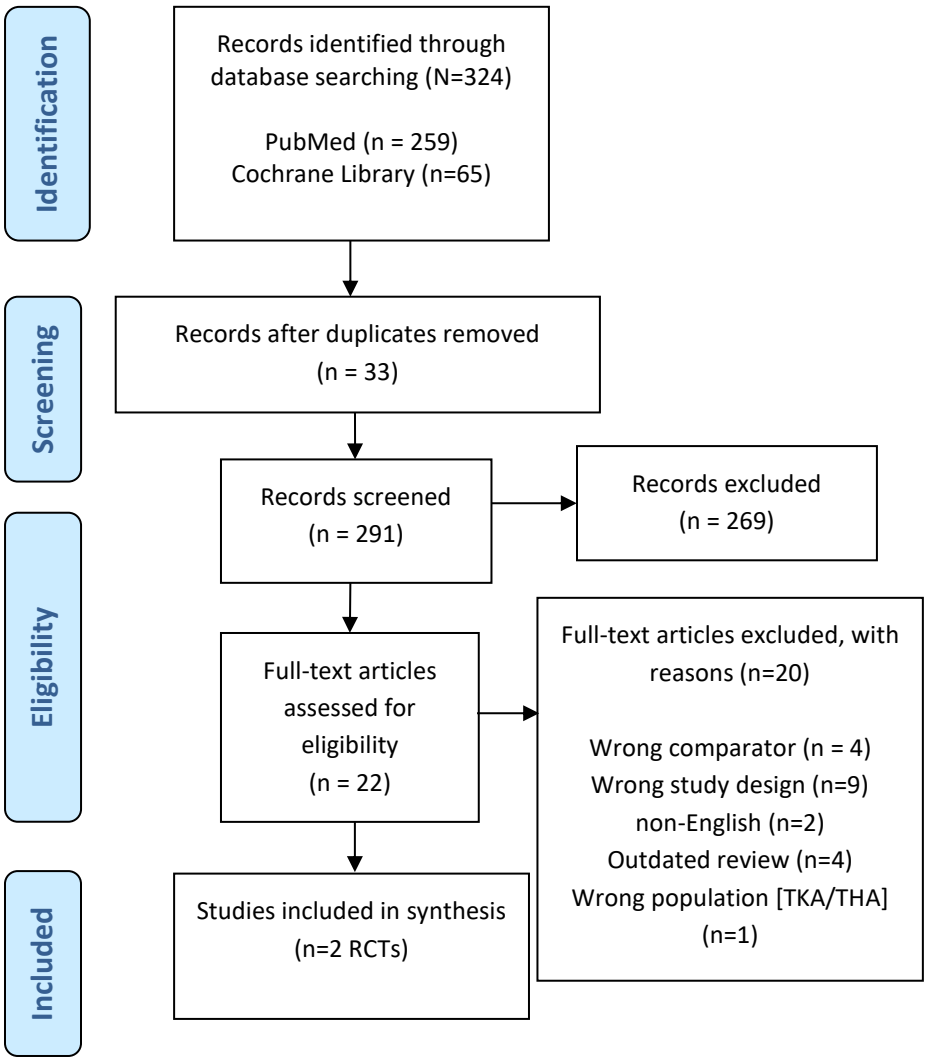


Figure 1: PRISMA flow diagram of included records

DESCRIPTION AND APPRAISALS OF TRIALS

We identified two eligible trials conducted in Canada, and USA which investigated the efficacy and safety of aspirin compared to LMWH for VTE prophylaxis in 12 540 adult patients with trauma-related operative (extremity) fractures or any trauma-related pelvic or acetabular fractures (18-19). In both trials, 81mg oral aspirin was given twice a day in the intervention arm, while 30mg enoxaparin was given subcutaneously twice daily in the control arm. The trials reported on mortality, DVT, PE and major bleeding.

The dose of enoxaparin was the standard in North America where these trials were conducted and is a dose which has been used in many previous studies (8,9) This differs from the dosing in South Africa for prophylaxis of 40mg daily. The dosing of aspirin in this study was given twice daily to match the enoxaparin so that one arm would be no less likely to adhere to their treatment regimen than the other due to dosing frequency.

Our risk of bias assessment showed low risk of bias (Figure 4). We noted lack of blinding in the two trials of both patients and healthcare providers. However, this is unlikely to result in serious risk of bias due to the objective outcomes reported and blinding of outcome assessors (18-19).

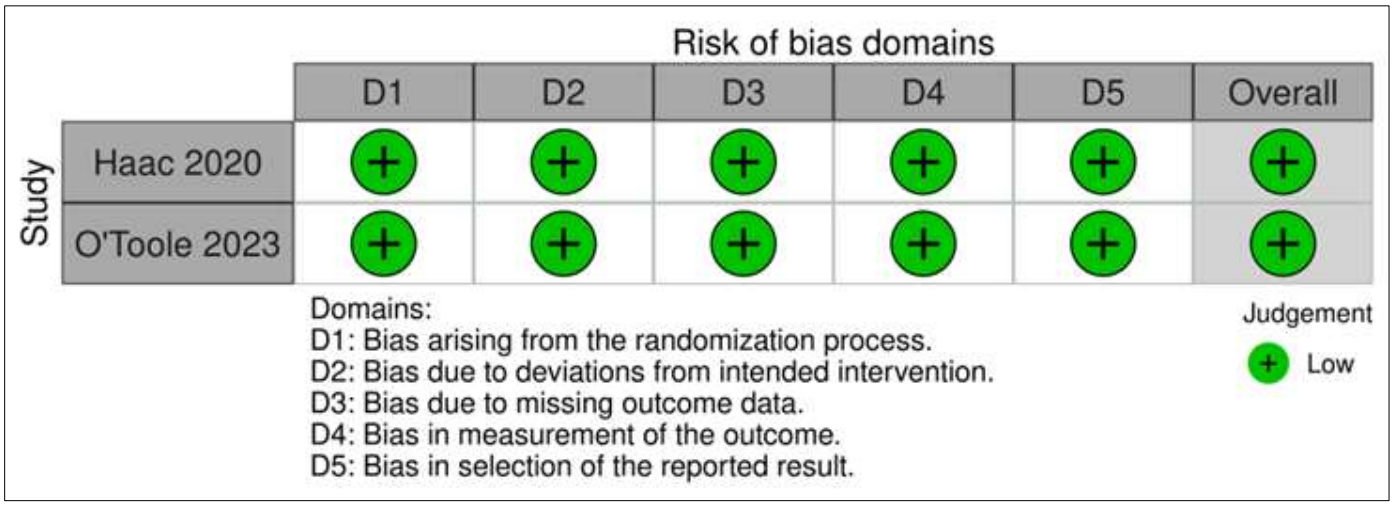


Figure 2: Risk of bias 2.0 of included trials

The O'Toole trial excluded potential participants prior to randomisation at the discretion of the treating clinician without reasons given; this accounted for 11% of excluded participants (Supplementary table S1). The overall total number of potential participants excluded with no reason was 19% (Supplementary table S2). We cannot rule out that this may have excluded higher-risk participants. There is no reason to believe that the higher risk patients who may have been excluded were excluded because of the study arm allocation or that there was selection bias.

Prevalence of risk factors for VTE in the study population showed that 0.7% had a previous VTE, 2.3% had cancer, 8.1% were diabetic and 34.5% were smokers. The average age of the study population was 44.5 years. Other risk factors were not captured in baseline characteristics table and therefore no data were available on the proportion of participants categorised as obese (Appendix 4). Under-representation of the elderly, no data on obesity and other risk factors and few participants with previous VTE, support our concern that this study population may consist of lower risk participants on average, and should therefore only be generalised to those at low to moderate risk of VTE. There were no data available on the risk factors of the patients who had been excluded. There was also no comparison between high-risk subgroups.

EFFECTS OF INTERVENTION

The GRADE Evidence Profile summarises the effects of aspirin compared to LMWH for each of the outcomes with explanation of the GRADE assessment (Appendix 3). Of note, Haac et al 2020 (18) reported composite endpoints of bleeding complications, deep surgical site infection, deep vein thrombosis, pulmonary embolism, and death within 90 days of injury. In the time to event analysis, the trial reported that "the cumulative weighted probability of being event-free at 90-days post-fracture was 97.8% (95% CI, 95.5–1.00%) in the aspirin group and 98.5% (95% CI, 96.6–1.00%) in the LMWH group". For the purposes of this rapid review, we extracted the unweighted outcomes to enable meta-analyses.

Table 2: Summary of findings table of comparison: Aspirin *vs.* LMWH

Aspirin compared to LMWH for VTE

Outcomes (Overall)	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with LMWH	Risk difference with Aspirin
Mortality	12540 (2 RCTs)	⨁⨁⨁⨁ High[a]	**RR 1.07** (0.71 to 1.59)	7 per 1,000	**1 more per 1,000** (2 fewer to 4 more)
Pulmonary embolism	12540 (2 RCTs)	⨁⨁⨁⨁ High[a,b]	**RR 0.77** (0.30 to 1.94)	15 per 1,000	**4 fewer per 1,000** (11 fewer to 14 more)
Deep vein thrombosis	12540 (2 RCTs)	⨁⨁⨁⨁ High[a]	**RR 1.48** (1.16 to 1.89)	17 per 1,000	**8 more per 1,000** (3 more to 15 more)
Rate of major bleeding	12540 (2 RCTs)	⨁⨁⨁⨁ High[a]	**RR 0.96** (0.89 to 1.05)	147 per 1,000	**6 fewer per 1,000** (16 fewer to 7 more)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. The O' Toole trial excluded potential participants prior to randomisation at the discretion of the treating clinician, without reasons given - this accounted for 11% of excluded participants (Supplementary table S1). In addition, overall total number of potential participants excluded with no reason was 19% (supplementary table S2). We can't rule out that this may have excluded higher risk participants, and therefore not fully representative of the patient population in our setting. We noted lack of blinding in both trials, however, this is unlikely to result in serious risk of bias. (O'Toole and Haac trials).
b. We did not downgrade imprecision; however, we noted that the absolute effects ranges from 11 fewer events to 14 more events of pulmonary embolism. A different clinical decision may be made at the extremes of this range.

- **Mortality**

Overall, the Haac 2020 and O'Toole et al., 2023 trials found that there is little difference in mortality when comparing aspirin to LMWH, risk ratio (RR) 1.07 (95% CI 0.72 to 1.59), n=12 540, moderate certainty evidence (Figure 9). There are 7 deaths per 1,000 in the enoxaparin group, with 1 more per 1,000 in the aspirin group (95% CI 2 fewer to 4 more events).

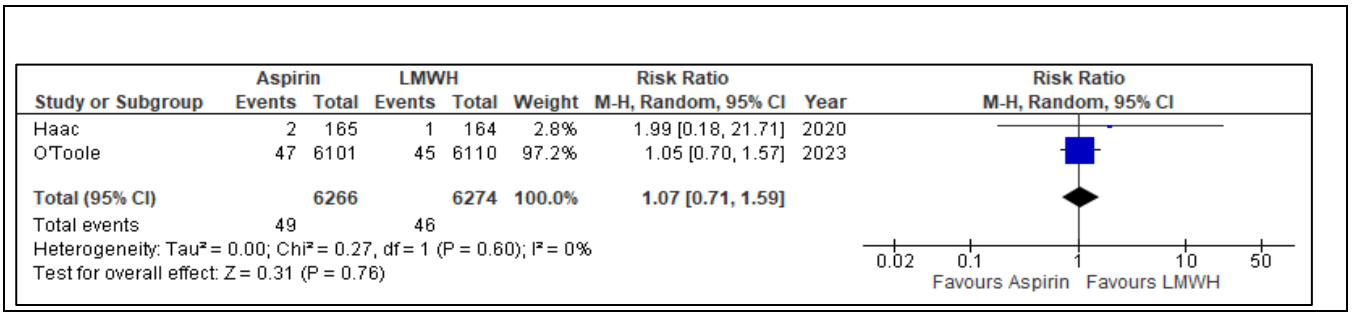


Figure5: Forest plot of Aspirin vs LMWH, outcome: Mortality

- **Pulmonary embolism**

Overall, the Haac, 2020 and O'Toole et al., 2023 trials found that aspirin compared to LMWH probably results in little difference in the risk of development of pulmonary emboli RR 0.77 (95% CI 0.30 to 1.94), n = 12 540, moderate certainty evidence due to imprecision (Figure 10). In the enoxaparin group, there are 15 per 1,000 pulmonary emboli, and there may be 4 fewer events per 1,000 in the aspirin group (95% CI 11 fewer events to 14 more events per 1,000).

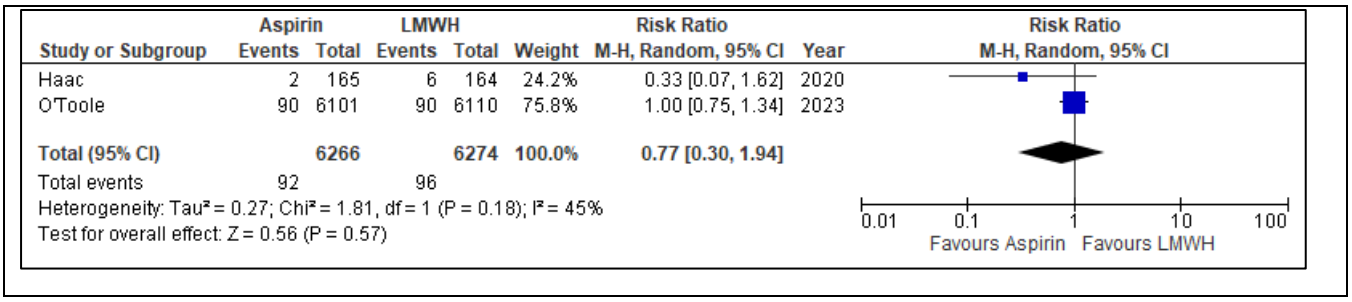


Figure6: Forest plot of Aspirin vs. LMWH, outcome: Pulmonary embolism

- **Symptomatic deep vein thrombosis**

Overall, the Haac, 2020 and O'Toole et al., 2023 trials found that aspirin compared to LMWH results in a small increased risk of DVT, RR 1.48 (95% CI 1.16 to 1.89), n = 12 540, moderate certainty evidence. (Figure 11). There were 17 per 1,000 events of symptomatic DVT in the LMWH group, with 8 more per 1,000 when aspirin given (95% CI 3 more to 15 more). This equated to a difference of 0.80 (95% CI 0.28-1.31) in the intention to treat (ITT) analysis and 0.57 (95% CI 0.08-1.07) in the per protocol (PP) analysis. When looking more closely at the proximal and distal DVT subgroups, there is no significant difference in the proximal DVTs in the ITT analysis; 0.25 (95% CI -0.12;0.62) or PP analysis; 0.04 (95% CI -0.30;0.39) (Appendix 6). The difference in distal DVTs was significant in both analyses (0.58 (95% CI 0.20;0.96) and 0.49 (0.12;0.86) respectively) favouring enoxaparin. In certain settings, risk stratification is used to determine whether distal DVTs will be actively managed with anticoagulation as

patients at low risk of embolization may be managed conservatively with serial ultrasound checks. This is due to their more favourable outcomes with lower rates of complication (22).

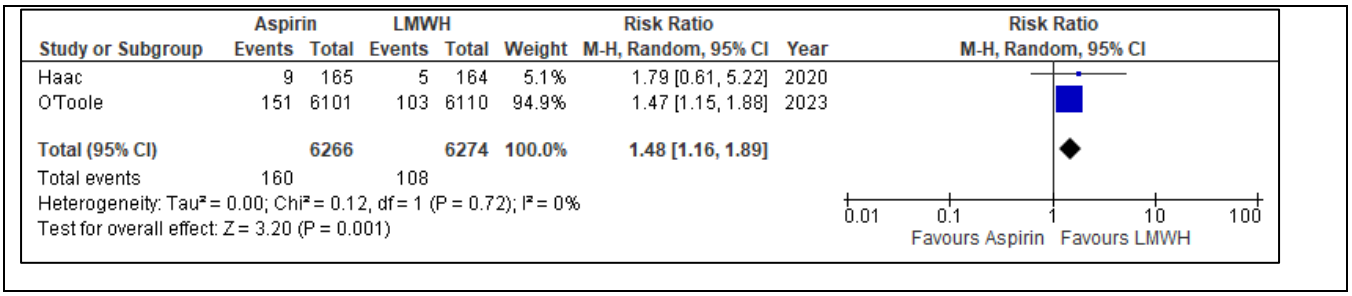


Figure7: Forest plot of Aspirin vs LMWH, outcome: Deep vein thrombosis

- **Rate of major bleeding**

Overall, the Haac, 2020 and O'Toole et al., 2023 trials show that aspirin compared to LMWH results in little or no difference in the rate of major bleeding RR 0.96 (95% CI 0.89 to 1.05), n=12 540, moderate certainty evidence (Figure 12). There are 147 per 1,000 major bleeding events in the LMWH group, with 6 fewer per 1,000 when aspiring given (95% CI 16 fewer to 7 more events).

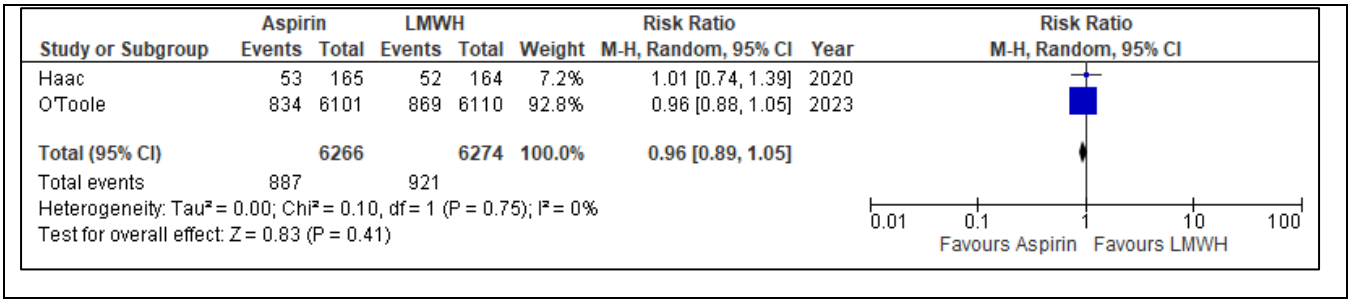


Figure8: Forest plot of Aspirin vs LMWH, outcome: Major bleeding

CONCLUSION

In people requiring venous thromboembolism prophylaxis following trauma-related operative (extremity) fracture and any trauma-related pelvic or acetabular fracture, there is likely little difference in the efficacy of aspirin compared to enoxaparin in terms of mortality, pulmonary embolism and the rate of major bleeding.

However, there is an increase in the risk of symptomatic DVT with aspirin use compared to enoxaparin in this patient population. The absolute risk is small at 8 additional cases of DVT per 1000 patients treated. The excess cases of DVT did not translate into increased risk of pulmonary embolism or death, and therefore aspirin may be a viable option for VTE prophylaxis in this patient population.

The enoxaparin dosing used in these trials (30mg 12hrly) is higher than the South African standard prophylactic dose of 40mg daily. The aspirin dose which we can consider using in South African public sector is 150mg daily, which is very marginally less than the total 162mg daily used in the study. It is possible that the difference in incidence of symptomatic DVT between aspirin and enoxaparin will therefore be less, but we do not have any data using doses of 40mg enoxaparin vs 150mg aspirin.

It is important to note that this study population may have been at low to moderate risk for VTE, as a large proportion (19%) of the screened participants were excluded without reason; 11% of 19% at the clinician's discretion... Some reported characteristics of the study population demonstrated the study prevalence of additional risk factors where 0.7% had a previous VTE, 2.3% had cancer, 8.1% were diabetic and 34.5% were smokers. The average age of the study population was 44.5 years and there were no data available on the proportion of participants categorised as obese. Under-representation of the elderly, no data on obesity prevalence and few participants with previous VTE support our concern that this study population may consist of lower risk participants on average, and should therefore only be generalised to those at low to moderate risk of VTE. There were no data available on the risk factors of the patients who had been excluded. There was also no comparison between high-risk subgroups.

Importantly however, aspirin may provide significant cost savings, increased access to VTE prophylaxis and enable earlier patient discharge from facilities. These potential benefits may still have a big impact, even if used only in the low-risk portion of patients with trauma-related operative (extremity) fractures and any trauma-related hip or acetabular fractures.

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*	The certainty of the evidence is moderate. The primary concern was in the O' Toole trial where 19% of excluded patients were excluded for reasons which are unclear. Characteristics of excluded patients are not described. This exclusion may have impacted the overall risk of VTE in the study population but there is no reason to believe that exclusion would have occurred differently between groups and thus risk of selection bias is low. We can only extrapolate these findings to patients at low to moderate risk of VTE for the above reasons. There was lack of blinding, however, the main outcomes of death, pulmonary embolism, deep vein thrombosis and major bleeding are objective and not likely to be affected by performance or detection bias.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☐ Small ☐ Interventions are similar in efficacy	Death: There are 7 deaths per 1,000 in the enoxaparin group, with 1 more per 1,000 in the aspirin group (95% CI 2 fewer to 4 more events). PE: In the enoxaparin group, there are 15 per 1,000 pulmonary emboli, and there may be 4 fewer events per 1,000 in the aspirin group (95% CI 11 fewer events to 14 more events per 1,000). Bleeding: There are 147 per 1,000 major bleeding events in the LMWH group, with 6 fewer per 1,000 when aspiring given (95% CI 16 fewer to 7 more events).
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	
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large ☐ Moderate ☐ Small ☒ None ☐	DVT: There were 17 per 1,000 events of symptomatic DVT in the LMWH group, with 8 more per 1,000 when aspirin given (95% CI 3 more to 15 more). We assessed the clinical significance of this finding as trivial as it did not result in an increased risk of DVT complications. PE's and deaths. There is no difference in the risk of PE or death in the aspirin group compared with enoxaparin.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☐ Favours control ☐ Intervention = Control ~~*or*~~ ~~Uncertain~~ ☒	The balance of effects favours either aspirin or enoxaparin. A dose of 150mg aspirin daily is equivalent to a twice daily dose of 81mg aspirin (162mg per day) as used in the trials included in this review. This is due to the similar daily dose and long half-life of aspirin meaning that plasma concentrations would not be significantly different.

<table>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available:</td><td>At the time of this review:
• Enoxaparin is currently included on the EML as the standard of care.
• DOACs especially rivaroxaban are under consideration for inclusion on the EML for this indication but a final decision has not yet been made.</td></tr>
<tr><td>FEASABILITY</td><td>Is implementation of this recommendation feasible?
Yes [x] No [ ] Uncertain [ ]</td><td>Both medicines are widely available.
Hospital discharge may be more feasible with an oral formulation versus a subcutaneous formulation.
The 300mg scored tablet is currently on tender – tablets would need to be halved for a 150mg dose.</td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive [ ] Less intensive [x] Uncertain [ ]</td><td>Enoxaparin 40mg/ day
Aspirin 150mg/ day (half of 300mg tablet)
Rivaroxaban 10mg/ day
DOACs outside of PICO but included for comparator purposes as currently under review for inclusion on the EML for this indication.
Note: Treatment costs relate to direct medicine costs only i.e. other costs related to length of hospital stay not reflected. In clinical practice duration of therapy is likely to be less than 14 days for the population under consideration.
*MHPL - 1 Sep 2023
**Weighted mean as per tender allocation
<table><tr><th colspan="4">Treatment regimen</th></tr><tr><th>Drug</th><th>Price/unit*</th><th>Duration (days)</th><th>Treatment Cost per patient</th></tr><tr><td>Enoxaparin 40mg OD</td><td>54.99</td><td>14</td><td>769.86</td></tr><tr><td>Rivaroxaban 10mg OD</td><td>14.66</td><td>14</td><td>205.17</td></tr><tr><td>Aspirin 150mg OD**</td><td>0.32</td><td>14</td><td>2.21 - 4.42</td></tr></table>Aspirin treatment cost for 7 days = R2.21. Assuming tender pack size of 14 X 300mg tablets issued per patient then cost = R4.42</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>Patients have been shown to prefer oral to subcutaneous VTE prophylaxis with a marginal utility of 0.16; 95% CI: 0.11 - 0.21, P<0.0001 (23).</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?
Yes [ ] No [ ] Uncertain [x]</td><td>The use of an oral medicine may make earlier discharge more feasible.</td></tr>
</table>

Version	Date	Reviewer(s)	Recommendation
Initial (v1.0)	12 October 2023	GT, NB, MM, ZA, SE, TK, MB	Aspirin to be used as prophylaxis in patients with operative trauma-related extremity fractures for all operative or non-operative hip and acetabular fractures. Recommended for use in patients at low to moderate risk of VTE

APPENDIX

Appendix 1a: Search Strategy PubMed (arthroplasty and fractures)

Search	Query	Results
#4	Search: Filters: from 2019/1/1 - 2023/6/2	259
#3	Search: #1 AND #2	1125
#2	Search: Thromboprophylaxis [tiab] OR Venous Thromboembolism Prophylaxis [tiab] OR VTE prophylaxis [tiab] OR Venous Thromboembolism [Mesh] OR embolism prevention [tiab] OR thrombosis prevention [tiab] OR deep vein thrombosis prevention [tiab] OR venous thrombosis prevention [tiab] OR Venous Thromboembolism prevention [tiab]	32915
#1	Search: Aspirin [Mesh] OR Acetylsalicylic Acid [tiab] OR aloxiprinum [tiab] OR Acylpyrin [tiab] OR Colfarit [tiab] OR disopril [tiab] OR Ecotrin [tiab] OR Easprin [tiab] OR Endosprin [tiab] OR Magnecyl [tiab] OR Micristin [tiab] OR Polopirin [tiab] OR Polopiryna [tiab] OR Solprin [tiab] OR Solupsan [tiab] OR Zorprin [tiab] OR Acetysal [tiab] OR Aspro clear [tiab]	52286

Appendix 1b: Search Strategy Cochrane

Search	Query	Results
#3	Search: #1 AND #2 Filters: from Jan 2019 – June 2023	64
#2	Search: Thromboprophylaxis:ti,ab OR "Venous Thromboembolism Prophylaxis":ti,ab OR VTE next prophylaxis:ti,ab OR [mh "Venous Thromboembolism"] OR embolism next prevention:ti,ab OR thrombosis next prevention:ti,ab OR "deep vein thrombosis" next prevention:ti,ab OR "Venous Thromboembolism" next prevention:ti,ab	2717
#1	Search: [mh Aspirin] OR Acetylsalicylic next Acid:ti,ab OR aloxiprinum:ti,ab OR Acylpyrin:ti,ab OR Colfarit:ti,ab OR disopril:ti,ab OR Ecotrin:ti,ab OR Easprin:ti,ab OR Endosprin:ti,ab OR Magnecyl:ti,ab OR Micristin:ti,ab OR Polopirin:ti,ab OR Polopiryna:ti,ab OR Solprin:ti,ab OR Solupsan:ti,ab OR Zorprin:ti,ab OR Acetysal:ti,ab OR "Aspro clear":ti,ab	8172

Appendix 2: Characteristics of included studies

Citation	Study design	Population	Treatments	Main outcome
Haac BE, O'Hara NN, Manson TT, Slobogean GP, Castillo RC, O'Toole RV, Stein DM, ADAPT Investigators. Aspirin versus low-molecular-weight heparin for venous thromboembolism prophylaxis in orthopaedic trauma patients: a patient-centered randomized controlled trial. PLoS One. 2020 Aug 3;15(8): e0235628. (ADAPT trial)	Design: 1:1 open label randomized clinical trial Follow up: 90 days Country: Maryland, USA	Sample size: N=329, n= 164 Enoxaparin *vs.* aspirin n=165 Mean (SD) age: 45.4 (20.4) Enoxaparin *vs.* Aspirin 48.0 (18.6) Surgical procedure: Operative extremity fracture, or a pelvis or acetabular fracture	Intervention: enoxaparin at 30-mg, twice daily (oral, rectal, or via any other form of enteral access) Control: aspirin at 81-mg twice daily (oral, rectal, or via any other form of enteral access) Duration of treatment not reported.	1. Mortality 2. Composite DVT 3. Composite PE 4. Composite major bleeding
O'Toole 2023: Major Extremity Trauma Research Consortium (METRC). Aspirin or Low-Molecular-Weight Heparin for Thromboprophylaxis after a Fracture. New England Journal of Medicine. 2023 Jan 19;388(3):203-13. (PREVENT CLOT Trial)	Design: 1:1 pragmatic, multicenter, randomized, noninferiority trial Follow up: 90 days Country: 21 trauma centers in the United States and Canada	Sample size: N=12 211, Aspirin n=6101, Enoxaparin n=6110 Mean age (±SD) age: 44.6±17.8 years Surgical procedure: Patients who had an extremity fracture operatively or a fracture of the pelvis or acetabulum that was treated operatively or nonoperatively.	Intervention: Aspirin 81 mg twice daily (oral) Control: Enoxaparin at 30mg twice daily (subcutaneous) Duration of treatment not reported.	1. Death from any cause of death Notes: Three grades of cause specific death were used: related to pulmonary embolism, possibly related to pulmonary embolism, and unlikely to be related to pulmonary embolism 2. Pulmonary embolism Notes: Nonfatal pulmonary embolism was also adjudicated by the committee and reported as any, massive, sub-massive, clinically significant, or asymptomatic and in a segmental or subsegmental location 3. DVT Notes: deep-vein thrombosis events were subclassified according to the proximal or distal location. 4.Bleeding events Notes: Bleeding events included symptomatic bleeding into a critical area or organ; bleeding that caused a drop in the hemoglobin level of 20 g per liter or more within a 24-hour period and led to a transfusion of two or more units of whole blood or red cells; or bleeding that led to reoperation

Appendix 3: Evidence profile for aspirin vs LMWH

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin	LMWH	Relative (95% CI)	Absolute (95% CI)		
Mortality												
2	randomised trials	not serious[a]	not serious	not serious	not serious	none	49/6266 (0.8%)	46/6274 (0.7%)	**RR 1.07** (0.71 to 1.59)	**1 more per 1,000** (from 2 fewer to 4 more)	⊕⊕⊕⊕ High	CRITICAL
Pulmonary embolism												
2	randomised trials	not serious[a]	not serious	not serious	not serious[b]	none	92/6266 (1.5%)	96/6274 (1.5%)	**RR 0.77** (0.30 to 1.94)	**4 fewer per 1,000** (from 11 fewer to 14 more)	⊕⊕⊕⊕ Moderate	CRITICAL
Deep vein thrombosis												
2	randomised trials	not serious[a]	not serious	not serious	not serious	none	160/6266 (2.6%)	108/6274 (1.7%)	**RR 1.48** (1.16 to 1.89)	**8 more per 1,000** (from 3 more to 15 more)	⊕⊕⊕⊕ High	CRITICAL
Rate of major bleeding												
2	randomised trials	not serious[a]	not serious	not serious	not serious	none	887/6266 (14.2%)	921/6274 (14.7%)	**RR 0.96** (0.89 to 1.05)	**6 fewer per 1,000** (from 16 fewer to 7 more)	⊕⊕⊕⊕ High	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. We downgraded for serious risk of bias due to selection bias: The O' Toole trial excluded potential participants prior to randomisation at the discretion of the treating clinician, without reasons given - this accounted for 11% of participants (Supplementary table S1). In addition, overall total number of potential participants excluded with no reason was 19% (supplementary table S2).We can't rule out that this may have excluded higher risk participants, favouring aspirin. We noted lack of blinding of in both trials, however, this is unlikely to result in serious risk of bias. (O'Toole and Haac trials).

b. We did not downgrade imprecision, however, we noted that the absolute effects ranges from 11 fewer events to 14 more events of pulmonary embolism. A different clinical decision may be made at these ranges of the effect estimate.

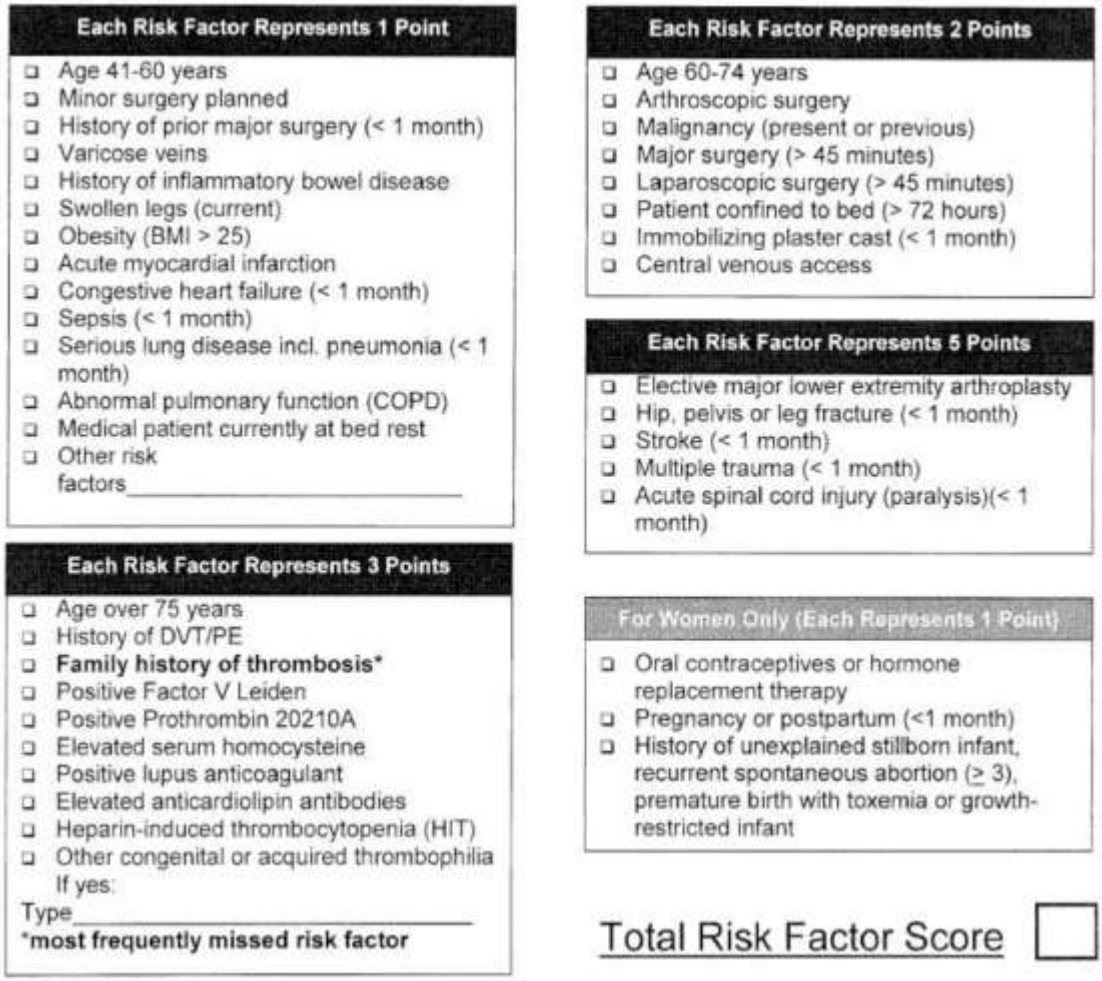
Appendix 4 : Supplementary Tab;e from O'Toole et al (19) (PREVENT CLOT) showing baseline characteristics including risk factors

Table S3. Baseline characteristics of the patients included in the per-protocol analysis*.

Characteristic	Aspirin N = 5505	Low-Molecular-Weight Heparin N = 5170	Overall N = 10,675
Age - years	44.5 ± 18.0	44.7 ± 17.6	44.6 ± 17.8
Male – no. (%)	3435 (62.4%)	3203 (62.0%)	6638 (62.2%)
Body mass index kg/m^2	27.1 (23.5, 31.7)	27.4 (23.7, 32.3)	27.2 (23.6, 32.0)
Race/Ethnicity – no. (%) κ			
Non-Hispanic White	3484 (63.3%)	3301 (63.8%)	6785 (63.6%)
Non-Hispanic Black	1071 (19.5%)	1009 (19.5%)	2080 (19.5%)
Hispanic	707 (12.8%)	627 (12.1%)	1334 (12.5%)
Other	193 (3.5%)	178 (3.4%)	371 (3.5%)
Risk factors – no. (%)			
Previous VTE	36 (0.7%)	35 (0.7%)	71 (0.7%)
Cancer	124 (2.3%)	148 (2.9%)	272 (2.5%)
Diabetes	444 (8.1%)	421 (8.1%)	865 (8.1%)
Smoking status$^{\delta}$			
Never smoked	2699 (49.0%)	2464 (47.7%)	5163 (48.4%)
Former smoker	904 (16.4%)	874 (16.9%)	1778 (16.7%)
Current smoker	1901 (34.5%)	1828 (35.4%)	3729 (34.9%)
Medications prior to injury – no. (%)			
Prior aspirin$^{\phi}$	451 (8.2%)	395 (7.6%)	846 (7.9%)
OCP/Estrogen$^{\Psi}$	100 (1.8%)	93 (1.8%)	193 (1.8%)
Plavix/Other antiplatelet agent$^{\lambda}$	45 (0.8%)	37 (0.7%)	82 (0.8%)
Health insurance – no. (%)$^{\Delta}$	4093 (74.4%)	3909 (75.6%)	8002 (75.0%)
Injury Severity Score [±]	9 (4–10)	9 (4–10)	9 (4–10)
Less than 9	2300 (42.0%)	2221 (43.1%)	4521 (42.5%)
9 to 15	2445 (44.6%)	2203 (42.8%)	4648 (43.7%)
More than 15	734 (13.4%)	724 (14.1%)	1458 (13.7%)
Injury regions – no. (%)[ε]			
Lower extremity	4829 (88.1%)	4513 (87.7%)	9342 (87.9%)
Upper extremity	1495 (27.3%)	1427 (27.7%)	2922 (27.5%)
Abdomen	661 (12.1%)	672 (13.1%)	1333 (12.5%)
Spine	528 (9.6%)	550 (10.7%)	1078 (10.1%)
Thorax	954 (17.4%)	982 (19.1%)	1936 (18.2%)
Neck	51 (0.9%)	61 (1.2%)	112 (1.1%)
Face	729 (13.3%)	752 (14.6%)	1481 (13.9%)
Head	693 (12.6%)	661 (12.8%)	1354 (12.7%)
Lower extremity fracture only	3698 (67.5%)	3431 (66.6%)	7129 (67.1%)
Upper extremity fracture only	650 (11.9%)	635 (12.3%)	1285 (12.1%)
Lower and upper extremity fractures	1131 (20.6%)	1082 (21.0%)	2213 (20.8%)

*Plus – minus values are means ±SD.
VTE venous thromboembolism, OCP oral contraceptive pill, IQR, interquartile range.
κ 1 patient with missing race data. An additional 104 patients refused to provide data.
δ 5 patients with missing smoking status.
ϕ 1 patient with missing prior aspirin data.
Ψ 2 patients with missing OCP/estrogen data.
λ. 1 patient with missing Plavix/other antiplatelet agent data.
Δ 1 patient with missing health insurance data.

Appendix 5: Caprini Risk Assessment Tool



Each Risk Factor Represents 1 Point

- ❑ Age 41-60 years
- ❑ Minor surgery planned
- ❑ History of prior major surgery (< 1 month)
- ❑ Varicose veins
- ❑ History of inflammatory bowel disease
- ❑ Swollen legs (current)
- ❑ Obesity (BMI > 25)
- ❑ Acute myocardial infarction
- ❑ Congestive heart failure (< 1 month)
- ❑ Sepsis (< 1 month)
- ❑ Serious lung disease incl. pneumonia (< 1 month)
- ❑ Abnormal pulmonary function (COPD)
- ❑ Medical patient currently at bed rest
- ❑ Other risk factors_____

Each Risk Factor Represents 2 Points

- ❑ Age 60-74 years
- ❑ Arthroscopic surgery
- ❑ Malignancy (present or previous)
- ❑ Major surgery (> 45 minutes)
- ❑ Laparoscopic surgery (> 45 minutes)
- ❑ Patient confined to bed (> 72 hours)
- ❑ Immobilizing plaster cast (< 1 month)
- ❑ Central venous access

Each Risk Factor Represents 3 Points

- ❑ Age over 75 years
- ❑ History of DVT/PE
- ❑ **Family history of thrombosis***
- ❑ Positive Factor V Leiden
- ❑ Positive Prothrombin 20210A
- ❑ Elevated serum homocysteine
- ❑ Positive lupus anticoagulant
- ❑ Elevated anticardiolipin antibodies
- ❑ Heparin-induced thrombocytopenia (HIT)
- ❑ Other congenital or acquired thrombophilia

If yes:

Type_____

***most frequently missed risk factor**

Each Risk Factor Represents 5 Points

- ❑ Elective major lower extremity arthroplasty
- ❑ Hip, pelvis or leg fracture (< 1 month)
- ❑ Stroke (< 1 month)
- ❑ Multiple trauma (< 1 month)
- ❑ Acute spinal cord injury (paralysis)(< 1 month)

For Women Only (Each Represents 1 Point)

- ❑ Oral contraceptives or hormone replacement therapy
- ❑ Pregnancy or postpartum (<1 month)
- ❑ History of unexplained stillborn infant, recurrent spontaneous abortion (≥ 3), premature birth with toxemia or growth-restricted infant

Total Risk Factor Score ☐

Appendix 6: Table 2 from O'Toole et al (19) showing the subgroups of proximal and distal DVTs.

Table 2. Primary and Secondary Outcomes.*

Outcome	Intention-to-Treat Population			Per-Protocol Population		
	Aspirin (N=6101)	Low-Molecular-Weight Heparin (N=6110)	Difference (CI)†	Aspirin (N=5505)	Low-Molecular-Weight Heparin (N=5170)	Difference (CI)†
	no. (% 90-day probability)		*percentage points*	*no. (% 90-day probability)*		*percentage points*
Primary outcome: death from any cause	47 (0.78)	45 (0.73)	0.05 (−0.27 to 0.38)‡	41 (0.75)	38 (0.72)	0.03 (−0.31 to 0.38)
Secondary efficacy outcome§						
Cause-specific death						
Death related to PE	4 (0.07)	5 (0.08)	−0.02 (−0.12 to 0.08)	4 (0.07)	3 (0.06)	0.01 (−0.08 to 0.11)
Death possibly related to PE	18 (0.30)	14 (0.22)	0.08 (−0.10 to 0.27)	14 (0.26)	10 (0.18)	0.08 (−0.10 to 0.26)
Death unlikely to be related to PE	29 (0.49)	31 (0.52)	−0.03 (−0.28 to 0.22)	27 (0.50)	28 (0.55)	−0.05 (−0.33 to 0.23)
PE type						
Any	90 (1.49)	90 (1.49)	0 (−0.43 to 0.43)	50 (0.92)	43 (0.84)	0.08 (−0.17 to 0.54)
Massive	1 (0.02)	3 (0.05)	−0.03 (−0.10 to 0.03)	0 (0.00)	2 (0.04)	−0.04 (−0.09 to 0.02)
Submassive	22 (0.36)	15 (0.25)	0.12 (−0.08 to 0.31)	11 (0.20)	10 (0.20)	0.01 (−0.16 to 0.18)
Clinically significant	61 (1.01)	64 (1.06)	−0.05 (−0.41 to 0.31)	34 (0.62)	26 (0.51)	0.11 (−0.17 to 0.40)
Asymptomatic	3 (0.05)	5 (0.08)	−0.03 (−0.12 to 0.06)	2 (0.04)	2 (0.04)	0 (−0.08 to 0.07)
Segmental	61 (1.01)	59 (0.98)	0.03 (−0.32 to 0.39)	36 (0.66)	26 (0.51)	0.15 (−0.14 to 0.44)
Subsegmental	38 (0.63)	40 (0.66)	−0.03 (−0.32 to 0.25)	23 (0.42)	22 (0.43)	−0.01 (−0.26 to 0.24)
DVT type						
Any	151 (2.51)	103 (1.71)	0.80 (0.28 to 1.31)	109 (2.01)	73 (1.44)	0.57 (0.08 to 1.07)
Proximal	74 (1.23)	59 (0.98)	0.25 (−0.12 to 0.62)	46 (0.85)	41 (0.81)	0.04 (−0.30 to 0.39)
Distal	87 (1.45)	52 (0.86)	0.58 (0.20 to 0.96)	65 (1.20)	36 (0.71)	0.49 (0.12 to 0.86)
Secondary safety outcome						
Bleeding complication	834 (13.72)	869 (14.27)	−0.54 (−1.78 to 0.69)	730 (13.30)	693 (13.44)	−0.14 (−1.43 to 1.16)
Wound complication	8 (0.13)	14 (0.23)	−0.10 (−0.25 to 0.05)	7 (0.13)	10 (0.20)	−0.07 (−0.22 to 0.09)
Infection	103 (1.73)	93 (1.55)	0.18 (−0.28 to 0.64)	100 (1.86)	69 (1.36)	0.50 (0.02 to 0.98)

* Percentages are calculated with the use of treatment-specific 90-day outcome probabilities, as calculated by a Kaplan–Meier estimator for the primary outcome and cumulative-incidence functions for the secondary outcomes, and do not use the group population as the denominator. This method was chosen over simple percentages to reflect the differential follow-up in some patients and for consistency with the treatment-effect estimates. DVT denotes deep-vein thrombosis, and PE pulmonary embolism.

† The confidence intervals are 95% confidence intervals for all the measures except death from any cause, for which 96.2% confidence intervals are shown.

‡ P<0.001 for noninferiority.

§ Because the statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for secondary or other outcomes, results are reported as point estimates and confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary outcomes.

Appendix 7: Subcategories of VTE Risk in Surgical and Non-Surgical Patients as per Standard Treatment Guidelines and Essential Medicines List for South Africa. Hospital Level, Adults, 2019 edition

SUBCATEGORIES OF VTE RISK IN SURGICAL AND NON-SURGICAL PATIENTS

	Surgical patients	*Medical patients*
Low VTE risk	» Surgery lasting <30 minutes » Injuries without or with only minor soft-tissue trauma » No or only minor additional predisposing risk factors	» Infection or acute inflammatory diseases without bed rest » Central venous catheters » No or only minor additional predisposing risk factors
Moderate VTE risk	» Surgical procedures of longer duration » Immobilisation of lower limb with plaster cast » Lower limb arthroscopic procedures. » No or only minor additional predisposing risk factors	» Acute cardiac insufficiency (NYHA III/IV) » Acute decompensated COPD without ventilation » Infection or acute inflammatory diseases with bed rest » Malignant disease » No or only minor additional predisposing risk factors
High VTE risk	» Major surgical procedures for malignancy » Multiple trauma or severe trauma of the spine, vertebra or » lower limbs » Major orthopaedic surgery, e.g. hip or knee replacement » Major surgical procedure of cardiothoracic and pelvic region	» Stroke with paralysis » Acute decompensated COPD with ventilation » Sepsis » ICU patients

Source: Jacobson BF, Louw S, Büller H, Mer M, de Jong PR, Rowji P, Schapkaitz E, Adler D, Beeton A, Hsu HC, Wessels P, Haas S; South African Society of Thrombosis and Haemostasis. Venous thromboembolism: prophylactic and therapeutic practice guideline. S Afr Med J. 2013 Feb 15;103(4 Pt 2):261-7.
https://www.ncbi.nlm.nih.gov/pubmed/23547704

References

1. Horlander KT, Mannino DM, Leeper KV. Pulmonary embolism mortality in the United States, 1979-1998: an analysis using multiple-cause mortality data. Archives of internal medicine. 2003;163(14):1711-7.
2. Heit JA, O'Fallon WM, Petterson TM, Lohse CM, Silverstein MD, Mohr DN, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. Archives of internal medicine. 2002;162(11):1245-8.
3. White RH, Zhou H, Romano PS. Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. Thrombosis and haemostasis. 2003;90(3):446-55.
4. White RH, Romano PS, Zhou H, Rodrigo J, Bargar W. Incidence and time course of thromboembolic outcomes following total hip or knee arthroplasty. Archives of internal medicine. 1998;158(14):1525-31.
5. Lobastov K, Urbanek T, Stepanov E, Lal B, Caprini J. The thresholds of Caprini score associated with increased risk of venous thromboembolism across different Specialties: a systematic review. Journal of Vascular Surgery: Venous and Lymphatic Disorders. 2023 Mar 1;11(2):453.
6. Montinari MR, Minelli S, De Caterina R. The first 3500 years of aspirin history from its roots - A concise summary. Vascular pharmacology. 2019;113:1-8.
7. Gómez-Outes A, Suárez-Gea ML, Lecumberri R, Terleira-Fernández AI, Vargas-Castrillón E. Direct-acting oral anticoagulants: pharmacology, indications, management, and future perspectives. Eur J Haematol. 2015;95(5):389-404.
8. Agnelli G. Prevention of venous thromboembolism in surgical patients. Circulation. 2004 Dec 14;110(24_suppl_1):IV-4.
9. Wall V, Fleming KI, Tonna JE, Nunez J, Lonardo N, Shipley RW, Nirula R, Pannucci CJ. Anti-factor Xa measurements in acute care surgery patients to examine enoxaparin dose. The American Journal of Surgery. 2018 Aug 1;216(2):222-9.
10. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ (Clinical research ed). 2017;358:j4008.
11. Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Assessing risk of bias in a randomized trial. Cochrane Handbook for Systematic Reviews of Interventions2019. p. 205-28.
12. Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Completing 'Summary of findings' tables and grading the certainty of the evidence. Cochrane Handbook for Systematic Reviews of Interventions2019. p. 375-402.
13. Anderson DR, Morgano GP, Bennett C, Dentali F, Francis CW, Garcia DA, et al. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. Blood Advances. 2019;3(23):3898-944.
14. Jiang Y, Du H, Liu J, Zhou Y. Aspirin combined with mechanical measures to prevent venous thromboembolism after total knee arthroplasty: a randomized controlled trial. Chinese medical journal. 2014;127(12):2201-5.
15. Kulshrestha V, Kumar S. DVT prophylaxis after TKA: routine anticoagulation vs risk screening approach - a randomized study. The Journal of arthroplasty. 2013;28(10):1868-73.
16. Westrich GH, Bottner F, Windsor RE, Laskin RS, Haas SB, Sculco TP. VenaFlow plus Lovenox vs VenaFlow plus aspirin for thromboembolic disease prophylaxis in total knee arthroplasty. The Journal of arthroplasty. 2006;21(6 Suppl 2):139-43.
17. Zou Y, Tian S, Wang Y, Sun K. Administering aspirin, rivaroxaban and low-molecular-weight heparin to prevent deep venous thrombosis after total knee arthroplasty. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis. 2014;25(7):660-4.

18. Haac BE, O'Hara NN, Manson TT, Slobogean GP, Castillo RC, O'Toole RV, et al. Aspirin versus low-molecular-weight heparin for venous thromboembolism prophylaxis in orthopaedic trauma patients: A patient-centered randomized controlled trial. PloS one. 2020;15(8):e0235628.
19. O'Toole RV, Stein DM, O'Hara NN, Frey KP, Taylor TJ, Scharfstein DO, et al. Aspirin or Low-Molecular-Weight Heparin for Thromboprophylaxis after a Fracture. The New England journal of medicine. 2023;388(3):203-13.
20. Sidhu VS, Kelly TL, Pratt N, Graves SE, Buchbinder R, Adie S, et al. Effect of Aspirin vs Enoxaparin on Symptomatic Venous Thromboembolism in Patients Undergoing Hip or Knee Arthroplasty: The CRISTAL Randomized Trial. Jama. 2022;328(8):719-27.
21. Farey JE, An VVG, Sidhu V, Karunaratne S, Harris IA. Aspirin versus enoxaparin for the initial prevention of venous thromboembolism following elective arthroplasty of the hip or knee: A systematic review and meta-analysis. Orthopaedics & traumatology, surgery & research : OTSR. 2021;107(1):102606.
22. Stevens SM, Woller SC, Kreuziger LB, Bounameaux H, Doerschug K, Geersing GJ, Huisman MV, Kearon C, King CS, Knighton AJ, Lake E. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report. Chest. 2021 Dec 1;160(6):e545-608.
23. (Haac BE, O'Hara NN, Mullins CD, et al. Patient preferences for venous thromboembolism prophylaxis after injury: a discrete choice experiment [published correction appears in BMJ Open. 2017 Dec 22;7(12):e016676corr1]. *BMJ Open*. 2017;7(8):e016676 10.1136/bmjopen-2017-016676)