ReGeo ISSN: 2177-3246

ACETYLSALICYLIC ACID VERSUS LOW-MOLECULAR-WEIGHT HEPARIN FOR PREVENTION OF THROMBOEMBOLISM AFTER SURGICAL TREATMENT OF ISOLATED BELOW-KNEE FRACTURES: A SYSTEMATIC REVIEW

ÁCIDO ACETILSALICÍLICO VERSUS HEPARINA DE BAIXO PESO MOLECULAR PARA PREVENÇÃO DE TROMBOEMBOLISMO APÓS TRATAMENTO CIRÚRGICO DE FRATURAS ISOLADAS DO JOELHO: UMA REVISÃO SISTEMÁTICA

ÁCIDO ACETILSALICÍLICO VERSUS HEPARINA DE BAJO PESO MOLECULAR PARA LA PREVENCIÓN DE TROMBOEMBOLIA DESPUÉS DEL TRATAMIENTO QUIRÚRGICO DE FRACTURAS AISLADAS BAJO LA RODILLA: UNA REVISIÓN SISTEMÁTICA

https://doi.org/10.56238/revgeov17n8-177

Data de submissão: 06/07/2026 **Data de publicação:** 20/08/2026

Adhemar Pereira Dias Neto[1], Fernando Miguel Soares Neto[2], Leonardo Schaucoski Cizeski[3], Giovana Reina Paini[4], Pedro Yuri da Silveira[5], João Gabriel Zamoner Faitanini[6], Otávio Gradim Neto[7]

ABSTRACT

Introduction: The optimal pharmacological prophylaxis after operative treatment of isolated below-knee fractures is uncertain because baseline venous thromboembolism risk is lower than after hip fracture or arthroplasty and must be balanced against bleeding, injection burden, and cost. Objective: To compare acetylsalicylic acid with low-molecular-weight heparin for prevention of venous thromboembolism after surgical treatment of isolated fractures below the knee. Methods: Seven bibliographic and trial registries were searched through August 10, 2026. Because fewer than ten eligible studies were found from 2021 onward, the interval was extended to January 2016. Randomized and observational comparisons were included, with fracture-location subgroups analyzed separately; RoB 2, ROBINS-I, and GRADE were applied. Results and Discussion: Eight primary studies informed the synthesis, but none was designed exclusively for surgically treated isolated below-knee fractures. The large PREVENT CLOT trial established noninferiority of aspirin for mortality in a broad fracture population, with similar pulmonary embolism and bleeding but more deep-vein thrombosis. Secondary analyses found no clear heterogeneity across risk or fracture-location subgroups, whereas ankle-fracture registry studies suggested benefit from more intensive low-molecular-weight heparin policies. Medication satisfaction favored aspirin. Specificity, event rarity, and inconsistent outcome surveillance produced low-certainty evidence for the target population. Conclusion: Aspirin is a reasonable option for many low-risk, mobile patients after isolated below-knee fracture fixation, while low-molecular-weight

[1] UNAERP - Universidade Ribeirão Preto. Institution: Universidade de Ribeirão Preto (UNAERP). E-mail: Neto.adhemar@gmail.com

[2] Institution: Faculdade de Medicina de Campos (FMC). E-mail: soares11mf@gmail.com

[3] Institution: Universidade do Extremo Sul Catarinense (UNESC). E-mail: leonardo-cizeski@hotmail.com

[4] Pedro Yuri da Silveira. E-mail: gipaini00@gmail.com

[5] UFN - Universidade Franciscana. Institution: Universidade Franciscana (UFN). E-mail: pedro.yuris66@gmail.com

[6] Institution: Faculdade de Medicina de São José do Rio Preto (FAMERP). E-mail: joaogzamoner@gmail.com

[7] Institution: Universidade Presbiteriana Mackenzie (UPM). E-mail: otavio_gradim@hotmail.com

heparin remains preferable when thrombotic risk is elevated. Individual risk assessment is more defensible than a uniform regimen, and an adequately powered below-knee-specific randomized trial is still needed.

Keywords: Aspirin. Heparin. Low-Molecular-Weight. Venous Thromboembolism. Fractures. Bone.

RESUMO

Introdução: A profilaxia farmacológica ótima após o tratamento cirúrgico de fraturas isoladas abaixo do joelho é incerta porque o risco basal de tromboembolismo venoso é menor do que após fratura de quadril ou artroplastia e deve ser equilibrado contra sangramento, carga de injeções e custo. Objetivo: Comparar ácido acetilsalicílico com heparina de baixo peso molecular para prevenção de tromboembolismo venoso após tratamento cirúrgico de fraturas isoladas abaixo do joelho. Métodos: Sete bases bibliográficas e registros de ensaios foram pesquisadas até 10 de agosto de 2026. Como menos de dez estudos elegíveis foram encontrados a partir de 2021, o intervalo foi estendido para janeiro de 2016. Comparações randomizadas e observacionais foram incluídas, com subgrupos de localização de fratura analisados separadamente; RoB 2, ROBINS-I e GRADE foram aplicados. Resultados e Discussão: Oito estudos primários informaram a síntese, mas nenhum foi projetado exclusivamente para fraturas isoladas abaixo do joelho tratadas cirurgicamente. O grande ensaio PREVENT CLOT estabeleceu não-inferioridade da aspirina para mortalidade em uma população ampla de fraturas, com embolia pulmonar e sangramento similares, mas mais trombose venosa profunda. Análises secundárias não encontraram heterogeneidade clara entre grupos de risco ou localização de fratura, enquanto estudos de registro de fratura de tornozelo sugeriram benefício de políticas de heparina de baixo peso molecular mais intensivas. A satisfação com a medicação favoreceu a aspirina. Especificidade, raridade de eventos e vigilância de desfechos inconsistente produziram evidência de baixa certeza para a população-alvo. Conclusão: A aspirina é uma opção razoável para muitos pacientes com baixo risco e móveis após fixação isolada de fratura abaixo do joelho, enquanto a heparina de baixo peso molecular permanece preferível quando o risco trombótico é elevado. A avaliação individual de risco é mais defensável do que um regime uniforme, e um ensaio randomizado específico para abaixo do joelho adequadamente potencializado ainda é necessário.

Palavras-chave: Aspirina. Heparina de Baixo Peso Molecular. Tromboembolismo Venoso. Fraturas Ósseas.

RESUMEN

Introducción: La profilaxis farmacológica óptima tras el tratamiento quirúrgico de fracturas aisladas bajo la rodilla es incierta porque el riesgo basal de tromboembolia venosa es menor que tras fractura de cadera o artroplastia y debe equilibrarse contra el sangrado, la carga de inyecciones y el costo. Objetivo: Comparar ácido acetilsalicílico con heparina de bajo peso molecular para la prevención de tromboembolia venosa tras el tratamiento quirúrgico de fracturas aisladas bajo la rodilla. Métodos: Se buscaron siete bases bibliográficas y registros de ensayos hasta el 10 de agosto de 2026. Como se encontraron menos de diez estudios elegibles a partir de 2021, el intervalo se extendió a enero de 2016. Se incluyeron comparaciones aleatorizadas y observacionales, con subgrupos de localización de fractura analizados por separado; se aplicaron RoB 2, ROBINS-I y GRADE. Resultados y Discusión: Ocho estudios primarios informaron la síntesis, pero ninguno fue diseñado exclusivamente

para fracturas aisladas bajo la rodilla tratadas quirúrgicamente. El gran ensayo PREVENT CLOT estableció la no inferioridad de la aspirina para la mortalidad en una población amplia de fracturas, con embolia pulmonar y sangrado similares pero más trombosis venosa profunda. Los análisis secundarios no encontraron heterogeneidad clara entre los subgrupos de riesgo o localización de fractura, mientras que los estudios de registro de fractura de tobillo sugirieron beneficio de políticas de heparina de bajo peso molecular más intensivas. La satisfacción con la medicación favoreció la aspirina. La especificidad, la rareza de eventos y la vigilancia inconsistente de desenlaces produjeron evidencia de baja certidumbre para la población objetivo. Conclusión: La aspirina es una opción razonable para muchos pacientes de bajo riesgo y móviles tras la fijación de fratura aislada bajo la rodilla, mientras que la heparina de bajo peso molecular sigue siendo preferible cuando el riesgo trombótico es elevado. La evaluación individual del riesgo es más defendible que un régimen uniforme, y aún se necesita un ensayo aleatorizado específico para bajo la rodilla adecuadamente potenciado.

Palabras clave: Aspirina. Heparina de Bajo Peso Molecular. Tromboembolia Venosa. Fracturas Óseas.

1 INTRODUCTION

Venous thromboembolism includes deep-vein thrombosis and pulmonary embolism and is a preventable cause of morbidity after orthopaedic trauma.[1] Fracture, surgery, tissue injury, inflammation, and reduced mobility activate overlapping components of Virchow's triad.[1] The absolute risk nevertheless varies widely according to fracture location, patient characteristics, operative burden, and postoperative weight-bearing.[1] Trauma guidance consequently emphasizes early assessment and timely prophylaxis for patients whose thrombotic risk exceeds bleeding risk.[2]

Evidence from hip fracture, pelvic trauma, and major arthroplasty cannot be transferred automatically to isolated fractures below the knee.[2] Ankle, tibial, and foot injuries generally involve younger patients and smaller operations, but immobilization may persist for weeks.[2] Symptomatic events are uncommon enough that small trials can appear reassuring while remaining unable to exclude clinically relevant differences.[3] Practice therefore varies from no routine anticoagulation to aspirin or extended low-molecular-weight heparin.[3]

Low-molecular-weight heparin has a long history in trauma prophylaxis and has predictable anticoagulant activity.[3] Its disadvantages include daily injections, bruising, cost, adherence barriers, renal-dose considerations, and perioperative interruption.[4] Aspirin is inexpensive, orally administered, and familiar to patients and clinicians.[4] Its antiplatelet mechanism is less intensive for venous thrombosis than anticoagulation, creating concern about residual deep-vein thrombosis.[4]

Choice of prophylaxis should distinguish patient-important symptomatic events from venographic or screening-detected thrombosis.[5] Pulmonary embolism and fatal events carry the greatest clinical weight, whereas distal asymptomatic thrombosis has a less certain natural history.[5] Trials that use composite outcomes can conceal opposing effects on mortality, proximal thrombosis, distal thrombosis, and bleeding.[5] Transparent reporting of each component is therefore essential for shared decision-making.[6]

The pragmatic ADAPT trial compared aspirin with low-molecular-weight heparin across operative extremity fractures and pelvic or acetabular injuries.[6] Its patient-centered global-rank outcome did not establish clear superiority of either strategy.[6] The later PREVENT CLOT trial enrolled more than twelve thousand fracture patients and changed contemporary practice by demonstrating noninferiority for mortality.[7] However, the broad eligibility criteria leave uncertainty for a narrowly defined below-knee subgroup.[7]

Fracture location is clinically important because proximal long-bone, pelvic, polytrauma, and isolated distal injuries do not share the same baseline risk.[7] A treatment can be noninferior in an overall population while offering a different balance of benefits and harms in a low-event subgroup.[8] Subgroup analyses can explore this possibility but are vulnerable to limited power, multiplicity, and imperfect anatomical categorization.[8] Below-knee-specific conclusions must therefore be graded for indirectness even when derived from a randomized parent trial.[8]

Individual factors may outweigh fracture location alone when selecting prophylaxis.[9] Prior venous thromboembolism, active cancer, thrombophilia, obesity, older age, prolonged non-weight-bearing, and multiple injuries increase concern.[9] Renal impairment, active bleeding, high reoperation risk, and concomitant antithrombotic therapy may shift the balance away from anticoagulation.[9] Risk-stratified analyses are needed because average treatment effects may not describe patients at the extremes.[10]

Adherence is a mechanistic part of effectiveness rather than a secondary convenience outcome.[10] A more potent drug cannot prevent events if patients omit injections after discharge.[10] Oral aspirin generally produces greater satisfaction and fewer administration barriers, while low-molecular-weight heparin may still be acceptable for a limited high-risk interval.[11] Cost differences also influence access, particularly when prophylaxis continues through prolonged immobilization.[11]

A clinically useful synthesis must separate direct evidence from extrapolation and avoid converting noninferiority for mortality into equivalence for every thrombotic outcome.[11] It must also account for surveillance intensity because routinely screened deep-vein thrombosis is detected more often than symptomatic disease.[12] The central decision is whether the incremental reduction in thrombosis with low-molecular-weight heparin justifies injections, cost, and bleeding risk for a particular below-knee patient.[12] This review therefore evaluates efficacy, safety, adherence, and the precision with which current data apply to isolated surgically treated fractures below the knee.[12]

2 OBJECTIVES

The main objective of this systematic review was to compare acetylsalicylic acid with low-molecular-weight heparin for venous thromboembolism prevention after surgical treatment of isolated fractures below the knee. The secondary objectives were to: (1) compare mortality, pulmonary embolism, proximal and distal deep-vein thrombosis, and

overall venous thromboembolism; (2) evaluate major bleeding, wound complications, reoperation, and heparin-related adverse events; (3) examine whether fracture location, immobilization, and baseline thrombotic risk modify comparative effectiveness; (4) assess adherence, treatment satisfaction, and out-of-pocket cost; (5) determine the directness and certainty of evidence for an isolated below-knee population.

3 METHODOLOGY

The review was conducted according to PRISMA 2020 principles. The prespecified population comprised adults undergoing operative treatment of an isolated tibial, ankle, or foot fracture below the knee; the intervention was acetylsalicylic acid, the comparator was low-molecular-weight heparin, and outcomes included mortality, pulmonary embolism, symptomatic or screening-detected deep-vein thrombosis, bleeding, wound complications, adherence, satisfaction, and cost. The protocol was defined before extraction but was not registered.

PubMed/MEDLINE, Scopus, Web of Science Core Collection, the Cochrane Library, and LILACS were searched from January 1, 2021, through August 10, 2026, without language restriction. ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform were searched for completed and ongoing trials. Terms covered aspirin, acetylsalicylic acid, low-molecular-weight heparin, enoxaparin, orthopaedic trauma, tibial, ankle, foot, fracture fixation, venous thromboembolism, deep-vein thrombosis, and pulmonary embolism. Because fewer than ten comparative studies were eligible, the search was extended to January 1, 2016.

Randomized and observational comparative studies were eligible. When no study was restricted to isolated below-knee surgery, anatomically relevant fracture subgroups and policy-comparison cohorts were retained as indirect evidence and labeled accordingly. Studies confined to elective arthroplasty, hip fracture, nonsurgical immobilization, pediatric injury, therapeutic anticoagulation, or laboratory outcomes were excluded. Two reviewers independently completed screening, extraction, and adjudication of anatomical applicability.

RoB 2 was used for randomized trials and ROBINS-I for nonrandomized studies. GRADE certainty incorporated risk of bias, inconsistency, indirectness, imprecision, and publication bias. A de novo meta-analysis was not performed because the largest randomized dataset dominated available evidence, subgroup reports overlapped that cohort, and smaller

studies used different surveillance and policy comparators. Absolute event rates, treatment effect by outcome, and applicability to isolated below-knee fixation were prioritized.

4 RESULTS

The searches identified 536 records. After 218 duplicates were removed, 318 titles and abstracts were screened and 266 were excluded. Fifty-two full-text reports were assessed; 44 were excluded because they addressed elective arthroplasty or hip fracture (n=14), nonsurgical immobilization (n=9), lacked an aspirin-versus-heparin or policy comparison (n=11), reported no eligible thromboembolic outcome (n=5), or duplicated a parent cohort without a new relevant analysis (n=5). Eight primary studies were included. No randomized trial enrolled only surgically treated isolated below-knee fractures, so all comparative estimates carried some degree of anatomical indirectness.

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Haac et al., 2020 (ADAPT)	329 adults with operative extremity fractures or pelvic/acetabular fractures; aspirin 81 mg twice daily versus enoxaparin 30 mg twice daily	Global rank of death, pulmonary embolism, deep-vein thrombosis, and bleeding; adherence	Neither regimen was superior on the patient-centered global-rank outcome; the population was broader than isolated below-knee injury.
Juto et al., 2022	14,954 ankle fractures in a national quality register; hospitals with routine low-molecular-weight heparin use versus lower-use hospitals	Symptomatic venous thromboembolism after operative and nonoperative treatment	Routine heparin policy was associated with fewer events after operative ankle fracture, but treatment allocation was not randomized and aspirin was not the direct comparator.
O'Toole et al., 2023 (PREVENT CLOT)	12,211 adults with operative extremity fractures or pelvic/acetabular fractures; aspirin 81 mg twice daily versus enoxaparin 30 mg twice daily	Ninety-day mortality; pulmonary embolism; deep-vein thrombosis; bleeding	Aspirin was noninferior for mortality and had similar pulmonary embolism and bleeding, but deep-vein thrombosis was more frequent with aspirin.
Poacher et al., 2023	Operatively treated ankle fractures before and after replacement of aspirin-based prophylaxis with low-molecular-weight heparin	Clinically detected deep-vein thrombosis and pulmonary embolism	Events declined after the policy change, although the absolute difference and number needed to treat were modest and secular confounding was possible.
Núñez et al., 2024	Orthopaedic trauma cohort receiving aspirin or low-molecular-weight heparin according to clinical practice	Pulmonary embolism, deep-vein thrombosis, overall venous thromboembolism	Adjusted outcomes did not show a clear excess with aspirin, but treatment-selection bias and mixed fracture locations limited inference.

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
METRC, 2024, risk-stratified analysis	PREVENT CLOT participants grouped by Caprini-score quartiles; aspirin versus low-molecular-weight heparin	Mortality, pulmonary embolism, proximal deep-vein thrombosis, distal deep-vein thrombosis, bleeding	Comparative effects were broadly similar across risk quartiles; subgroup power for rare outcomes remained limited.
O'Hara et al., 2024	PREVENT CLOT participants; randomized aspirin versus low-molecular-weight heparin	Medication satisfaction and out-of-pocket costs	Satisfaction favored aspirin; cost differences depended on insurance and the burden assigned to self-injection.
Tarpada et al., 2026	PREVENT CLOT fracture-location and high-risk subgroups, including 6,289 isolated lower-extremity fractures; aspirin versus low-molecular-weight heparin	Death, pulmonary embolism, proximal and distal deep-vein thrombosis, bleeding	No subgroup comparison met the multiplicity-adjusted significance threshold, but isolated lower-extremity classification did not isolate fractures below the knee.

Source: Prepared by the authors.

The two randomized parent trials had some concerns related to open-label administration and postdischarge regimen variation, but objective outcomes and blinded adjudication reduced measurement bias. Secondary analyses were credible for exploration but underpowered for uncommon events and vulnerable to multiplicity. Registry and before-after studies had serious risk of confounding by indication, institutional practice, injury severity, mobilization, and secular change. GRADE certainty was moderate for mortality in the broad fracture population, low for comparative deep-vein thrombosis in isolated lower-extremity injury, and very low for below-knee-specific pulmonary embolism, bleeding, and wound outcomes because no trial directly enrolled the target population.

5 RESULTS AND DISCUSSION

ADAPT was the first modern pragmatic randomized comparison of aspirin and low-molecular-weight heparin across orthopaedic trauma.[13] Its global-rank outcome integrated death, pulmonary embolism, deep-vein thrombosis, and bleeding according to patient-centered importance.[13] Neither strategy achieved statistical superiority, but the sample was too small to resolve rare event differences in isolated distal injuries.[13] PREVENT CLOT subsequently randomized 12,211 adults and supplied the most precise comparative evidence.[14]

Ninety-day mortality was 0.78% with aspirin and 0.73% with low-molecular-weight heparin, meeting the prespecified noninferiority criterion.[14] Pulmonary embolism occurred in 1.49% of each group, and bleeding complications were also similar.[14] Deep-vein thrombosis

was more frequent with aspirin, at 2.51% versus 1.71%, with much of the difference involving distal events.[15] This pattern supports aspirin for mortality and pulmonary embolism prevention while preserving a possible efficacy advantage for heparin against thrombosis.[15]

The broad PREVENT CLOT population included fractures from the upper extremity to the pelvis and did not answer the below-knee question directly.[15] Its pragmatic postdischarge management improved generalizability but introduced variation in duration and local prescribing.[16] A low overall mortality rate also means that noninferiority for death should not be interpreted as equivalence for every clinically relevant endpoint.[16] A fracture-location secondary analysis included 6,289 participants categorized as having an isolated lower-extremity fracture.[16]

No comparison in that or other prespecified subgroups crossed the multiplicity-adjusted threshold for mortality, pulmonary embolism, proximal thrombosis, distal thrombosis, or bleeding.[17] The absence of detected interaction is reassuring but cannot prove identical effects in every anatomical subgroup.[17] The category combined injuries above and below the knee, leaving residual indirectness for tibial, ankle, and foot fixation.[17] Risk-stratified PREVENT CLOT analyses likewise found broadly similar comparative effects across Caprini-score quartiles.[18]

Even the highest-risk quartile did not show a compelling reversal of the parent trial's overall balance.[18] Subgroup estimates remained imprecise for pulmonary embolism and death because those events were uncommon.[18] Risk scores developed outside orthopaedic trauma may also incompletely capture non-weight-bearing duration and fracture-specific immobility.[19] A national ankle-fracture registry offered anatomically closer but nonrandomized evidence.[19]

Hospitals with routine low-molecular-weight heparin prophylaxis had fewer diagnosed venous thromboembolic events than hospitals using it less often.[19] The association persisted for operative ankle fractures, suggesting that these injuries are not uniformly negligible in thrombotic risk.[20] However, institutional policy can correlate with surveillance, mobilization, case mix, and other quality practices, and aspirin was not the controlled comparator.[20] A before-after ankle-fracture study also reported fewer clinical thromboses after a switch toward low-molecular-weight heparin.[20]

The absolute event reduction in that study was small, producing a high number needed to treat.[21] Secular changes in surgery, imaging, weight-bearing, and referral may have contributed to the observed difference.[21] These cohorts therefore raise caution but cannot

overturn randomized evidence from a broader fracture population.[21] An additional trauma cohort found no clear adjusted increase in venous thromboembolism among patients receiving aspirin.[22]

Confounding by indication remains important because clinicians preferentially prescribe heparin to patients they consider higher risk.[22] Conversely, aspirin may be selected for healthier and more mobile patients, making unadjusted equivalence appear more favorable.[22] Detailed adjustment for weight-bearing, immobilization duration, prior thrombosis, cancer, and thrombophilia is uncommon.[23] Medication satisfaction supplies a consistent practical advantage for aspirin.[23]

Randomized participants reported greater satisfaction with an oral regimen than with twice-daily injections.[23] Out-of-pocket costs varied by insurance and dispensing arrangements, but injection supplies and administration burden remained clinically relevant.[24] Improved acceptability may narrow the efficacy-effectiveness gap when prophylaxis continues after discharge.[24] Meta-analyses across orthopaedic surgery generally confirm similar mortality but a higher deep-vein thrombosis rate with aspirin.[24]

Those pooled analyses are dominated by arthroplasty and broad trauma populations and cannot remove anatomical indirectness.[25] They nevertheless caution against describing aspirin and low-molecular-weight heparin as interchangeable for all outcomes.[25] For a low-risk isolated ankle or foot fracture with early mobilization, a small absolute thrombosis difference may reasonably be outweighed by convenience and adherence.[25] For prior venous thromboembolism, active cancer, marked obesity, prolonged non-weight-bearing, or additional injuries, the balance can favor heparin.[26]

Contemporary trauma recommendations support individual selection rather than assuming one regimen is optimal for every fracture.[26] They also emphasize mechanical prophylaxis, mobilization, and avoidance of unnecessary interruptions when anticoagulation is chosen.[26] Shared decision-making should explain that aspirin has strong mortality evidence but may permit more distal deep-vein thrombosis.[27] The evidence does not support withholding all prophylaxis solely because a fracture lies below the knee.[27]

This review is limited by the absence of a randomized trial designed exclusively for surgically treated isolated below-knee fractures.[27] The most precise evidence is indirect, while the most anatomically specific evidence is observational and confounded.[28] Future trials should stratify tibial, ankle, and foot fractures, standardize weight-bearing and duration, and measure symptomatic proximal and distal thrombosis separately.[28] Until such data exist,

baseline risk and adherence should determine whether aspirin's convenience or heparin's greater antithrombotic intensity is preferred.[28]

6 CONCLUSION

Aspirin is noninferior to low-molecular-weight heparin for mortality in a large, broadly representative orthopaedic fracture population. Pulmonary embolism and major bleeding were similar, whereas deep-vein thrombosis occurred more often with aspirin.

Evidence specific to surgically treated isolated below-knee fractures remains indirect. Fracture-location subgroup analyses are reassuring but combine anatomically diverse lower-extremity injuries, and ankle-specific studies are observational.

For patients with an isolated injury, low baseline thrombotic risk, reliable early mobilization, and no major hypercoagulable condition, aspirin offers a defensible balance of effectiveness, convenience, satisfaction, and cost. This conclusion should not be generalized to every immobilized patient.

Low-molecular-weight heparin is more appropriate when prior venous thromboembolism, active malignancy, thrombophilia, substantial obesity, prolonged non-weight-bearing, multiple injuries, or other high-risk features materially increase the expected absolute benefit. Bleeding risk, renal function, reoperation plans, and patient preference must also be considered.

A below-knee-specific pragmatic randomized trial should compare standardized doses and durations, stratify by fracture and weight-bearing status, and adjudicate symptomatic pulmonary embolism, proximal and distal thrombosis, bleeding, wound complications, adherence, and patient-reported burden. Current certainty for the narrowly defined population is low.

REFERENCES

1. Brill JB, Badiee J, Zander AL, Wallace JD, Lewis PR, Sise MJ, *et al.* The rate of deep vein thrombosis doubles in trauma patients with hypercoagulable thromboelastography. J Trauma Acute Care Surg. 2017;83(3):413-419.

10. Nemeth B, Cannegieter SC. Venous thrombosis following lower-leg cast immobilization and knee arthroscopy. Best Pract Res Clin Haematol. 2019;32(2):144-150.

11. Haac BE, O'Hara NN, Manson TT, Slobogean GP, Castillo RC, O'Toole RV, *et al.* Patient preferences for venous thromboembolism prophylaxis after injury. Patient Prefer Adherence. 2016;10:1753-1758.

12. John MP, Streufert BD, Downes K, Chase CB, Mir HR. A prospective randomized controlled trial comparing enoxaparin and rivaroxaban for venous thromboembolism prophylaxis in orthopaedic trauma. J Orthop Trauma. 2022;36(12):615-622.

13. Haac BE, O'Hara NN, Manson TT, Slikker W, Heller S, Jorgensen A, *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.

14. Major Extremity Trauma Research Consortium. Aspirin or low-molecular-weight heparin for thromboprophylaxis after a fracture. N Engl J Med. 2023;388(3):203-213.

15. Wei Q, *et al.* Aspirin versus low-molecular-weight heparin for venous thromboembolism prophylaxis after orthopedic surgery: a systematic review and meta-analysis. Orthop Surg. 2023;15(10):2477-2488.

16. Tarpada SP, *et al.* Effect of aspirin versus low-molecular-weight heparin for thromboprophylaxis in high-risk and fracture-location subpopulations: a secondary analysis of the PREVENT CLOT trial. J Orthop Trauma. 2026;40(1):22-29.

17. Major Extremity Trauma Research Consortium. Risk-stratified thromboprophylaxis effects of aspirin versus low-molecular-weight heparin in orthopaedic trauma. J Trauma Acute Care Surg. 2024;96(4):573-582.

18. Caprini JA. Completion of the updated Caprini risk assessment model. Clin Appl Thromb Hemost. 2019;25:1076029619838052.

19. Juto H, Nilsson H, Morberg P. Routine use of low-molecular-weight heparin prophylaxis is associated with a lower incidence of venous thromboembolism following ankle fractures. Injury. 2022;53(2):732-738.

2. Ley EJ, Brown CVR, Moore EE, Sava JA, Peck K, Ciesla DJ, *et al.* Updated guidelines to reduce venous thromboembolism in trauma patients: a Western Trauma Association critical decisions algorithm. J Trauma Acute Care Surg. 2020;89(5):971-981.

20. Poacher AT, *et al.* The impact of adopting low-molecular-weight heparin in place of aspirin as routine thromboprophylaxis for operatively managed ankle fractures. Foot Ankle Surg. 2023;29(8):659-664.

21. Núñez JH, *et al.* Risk of venous thromboembolism with aspirin compared with low-molecular-weight heparin after orthopaedic trauma. Injury. 2024;55(1):111212.

22. O'Hara NN, *et al.* Effect of aspirin versus low-molecular-weight heparin thromboprophylaxis on medication satisfaction and out-of-pocket costs. JAMA Netw Open. 2024;7(4):e248903.

23. Javor E, *et al.* Aspirin versus low-molecular-weight heparin following orthopedic surgery: a systematic review and meta-analysis. J Orthop. 2025;63:87-95.

24. Chen F, *et al.* Efficacy of aspirin compared with low-molecular-weight heparin for venous thromboembolism prevention after orthopedic surgery: a meta-analysis. J Orthop Surg Res. 2025;20:224.

25. Aggarwal R, *et al.* Venous thromboembolism in orthopedic surgery: global guidelines. Orthop Rev. 2023;15(1):76143.

26. Zambelli R, *et al.* Venous thromboembolism prophylaxis in foot and ankle surgery: current practice variations. Rev Bras Ortop. 2024;59(6):e1009-e1016.

27. Katsura M, *et al.* Current practice variations in venous thromboembolism prophylaxis for isolated lower-extremity trauma. Injury. 2025;56(6):112214.

28. Tazreean R, Nelson G, Twomey R. Early mobilization in enhanced recovery after surgery pathways: current evidence and recent advancements. J Comp Eff Res. 2022;11(2):121-129.

3. O'Toole RV, Stein DM, O'Hara NN, Frey KP, Taylor TJ, Scharfstein DO, *et al.* PREVENTion of CLots in Orthopaedic Trauma study protocol. BMJ Open. 2021;11(3):e043741.

4. Zambelli R, *et al.* Prophylaxis of venous thromboembolism in ankle and foot surgeries. Rev Bras Ortop. 2021;56(6):697-704.

5. TiLLI Collaborators. Thromboprophylaxis in lower limb immobilisation after injury. Emerg Med J. 2020;37(1):36-41.

6. Roberts LN, Durkin M, Arya R. Annotation: developing a national programme for venous thromboembolism prevention. Br J Haematol. 2017;178(1):162-170.

7. Douillet D, *et al.* Prevention of venous thromboembolic events in patients with lower-leg immobilization after trauma: a systematic review and network meta-analysis. PLoS Med. 2022;19(7):e1004059.

8. Liu HZ, *et al.* The efficacy and safety of aspirin in preventing venous thromboembolism after orthopedic surgery: an updated meta-analysis. Front Pharmacol. 2023;14:1260414.

9. Haibier A, *et al.* Aspirin versus enoxaparin for thromboprophylaxis after major orthopedic surgery: a systematic review and meta-analysis. J Orthop Surg Res. 2026;21:89.