RQ: Are low-dose heparin, aspirin, or apixaban equally effective alternatives to low molecular weight heparin (LMWH) for VTE prophylaxis following fixation of open fractures?

Section 1: Background

Venous thromboembolism (VTE), consisting of deep-vein thrombosis (DVT) and pulmonary embolism (PE), remains a major cause of morbidity, readmission, and mortality in orthopedic trauma surgery[1, 2]. Patients undergoing operative fixation for high-energy open fractures possess a hypercoagulable state driven by endothelial injury, local and systemic inflammation, and prolonged postoperative immobilization[3]. Historically, clinical guidelines have strongly favored injectable low-molecular-weight heparin (LMWH) over oral alternatives due to established efficacy in early trauma registries[3].

However, LMWH carries notable drawbacks such as high costs, logistical burdens of subcutaneous administration and risks of bleeding and heparin-induced thrombocytopenia[4]. Over the last few years, alternative prophylactic regimens, specifically cheap, accessible oral options like aspirin and direct oral anticoagulants (DOACs) like apixaban have generated immense clinical interest. While aspirin has been standard in elective arthroplasty, its efficacy in open fractures is highly debated[1]. The primary clinical gap centers on whether these oral alternatives provide equal therapeutic protection against fatal VTE events without worsening surgical-site bleeding or wound complications.

Section 2: Data Extraction Table

S.no	Author, year of publication, Country	Study Design	Sample Size	Study population (Inclusion and exclusion criteria)	Groups compared	Results
1	O'Toole et al.[2] (METRC), 2023, United States & Canada	Multi-center, randomized, trial (**PREVENT CLOT** Trial)	**Total: 12,211** • *Aspirin group:* n = 6,101 • *LMWH group:* n = 6,110	**Inclusion:** >18 years old with an extremity fracture (hip to midfoot, shoulder to wrist) treated operatively, or any pelvic/acetabular fracture. **Exclusion:** Primary nonoperative treatment, therapeutic anticoagulation required for pre-existing conditions, high bleeding risk contraindicating prophylaxis.	• **Aspirin:** 81 mg orally twice daily • **LMWH (Enoxaparin):** 30 mg subcutaneously twice daily	• **All-cause mortality at 90 days:** 0.78% (Aspirin) vs. 0.73% (LMWH), meeting the noninferiority margin (difference, 0.05 percentage points; 95% CI, -0.27 to 0.38). • **Pulmonary Embolism (PE):** 1.49% vs. 1.49% (identical). • **Deep-vein thrombosis (DVT):** 2.51% (Aspirin) vs. 1.71% (LMWH) — slightly higher in aspirin group. • **Bleeding complications/Infections:** No significant differences.

2	Nederpelt et al.[5], 2021, United States	Retrospective cohort study using the National Trauma Quality Improvement Program (**TQIP**) database	**Total: 4,560** (after 1:1 propensity score matching) • *DOAC group:* n = 2,280 • *LMWH group:* n = 2,280	**Inclusion:** Adult trauma patients admitted to TQIP centers with lower extremity fractures requiring chemical thromboprophylaxis. **Exclusion:** Age < 18, pre-existing therapeutic anticoagulation, missing prophylactic medication tracking.	• **DOACs** (primarily Apixaban or Rivaroxaban) • **LMWH** (Enoxaparin)	• **Symptomatic VTE rates:** Completely identical at **1.4%** in both the matched DOAC and LMWH groups ($p = 0.992$). • **Bleeding interventions:** Occurred less often in the DOAC group but statistically insignificant (5.8% vs 6.0%, $p = 0.772$). Concluded DOACs are a safe alternative.
3	Wu et al.[6], 2025, Global / Systematic Review	Systematic Review and Meta-Analysis	**Total: 5 primary studies** focusing on lower limb trauma / fracture populations	**Inclusion:** Randomized and high-quality clinical studies evaluating New Oral Anticoagulants (NOACs/DOACs) versus LMWH specifically for lower limb fractures. **Exclusion:** Studies exclusively addressing elective total hip or knee arthroplasty	• **DOACs** (Apixaban, Rivaroxaban) • **LMWH**	• **Overall VTE Prevention:** No statistically significant differences between LMWH and DOACs (OR = 0.42, 95% CI [0.16–1.11]). • **DVT Risk Reduction:** DOACs demonstrated a slight statistical superiority over LMWH specifically in reducing local deep-vein thrombosis within nonoperative or traumatic subsets without altering overall PE rates.

4	Thrombosis Canada Clinical Guides, 2026, Canada[7]	National Evidence-Based Practice Guideline	Consensus-driven synthesis of recent clinical trials, including PREVENT CLOT	Patients undergoing surgery for major lower extremity injuries, hip fractures, or pelvic fixations.	• **Aspirin** • **LMWH** • **DOACs**	• **Aspirin vs LMWH:** Validates that 90-day mortality and PE rates are statistically equivalent. *However, explicitly flags that aspirin alone is significantly less effective than LMWH at preventing nonfatal DVT events.* • **DOAC Note:** Mentions extended prophylaxis for hip fractures but cautions that high-quality trial data for DOACs in acute polytrauma remains sparse compared to LMWH.
5	Wisconsin TQIP Collaborative Guidelines, 2025, United States[8]	Regional Trauma Quality Improvement Consensus Recommendation	Multicenter trauma registry expert consensus panel	Adult hospitalized injured trauma patients requiring DVT prophylaxis.	• **LMWH** (Standard) •**Aspirin /DOACs** (Alternatives)	• **Timing and Agent:** Strongly recommends initiating chemical prophylaxis with LMWH within **12–24 hours** post-injury if no active hemorrhage is present. • **Open/Complex Fractures:** Flags complex, open lower extremity fractures as high-risk, recommending prioritizing LMWH over oral options during the hyperacute inpatient phase due to systemic inflammation.
6	Ley et al. (Western Trauma Association)[9], 2020, United States	National Evidence-Based Practice Guideline & Decision Algorithm	Expert consensus panel and iterative clinical trial synthesis	Adult trauma patients (>18 years old) requiring pharmacologic VTE prophylaxis.	• LMWH (Preferred standard) • Low-dose Unfractionated Heparin (UFH)	• **Preferred Standard:** Establishes early, weight-adjusted LMWH as superior to heparin for baseline trauma populations. • **Renal Failure Exception:** Explicitly mandates low-dose UFH (5,000 units SQ TID) as the primary alternative when LMWH is contraindicated due to severe renal impairment (CrCl< 30mL/min) or acute kidney injury.

Section 3: Results Summary Write-Up

After reviewing the literature, no high-quality studies specifically addressing open fractures were found. While there are reviews on thromboembolic events in gunshot[10] and war injuries, these cases involve scenarios quite different from civilian open fractures. The evidence quality is low, making it unsuitable for direct application here. Therefore, our recommendation is based on indirect evidence from broader trauma and fracture studies on anti-embolic prophylaxis, though this is a notable limitation that affects the strength of our recommendation.

The clinical evidence landscape for alternative antithrombotics compared with low-molecular-weight heparin (LMWH) for venous thromboembolism (VTE) prophylaxis after traumatic fracture fixation delineates a hierarchy among aspirin, direct oral anticoagulants (DOACs) such as apixaban, and conventional injectable heparins.

The primary clinical benchmark stems from the landmark, massive PREVENT CLOT trial which conclusively established that oral aspirin (81 mg twice daily) is noninferior to standard enoxaparin/LMWH (30 mg twice daily) for the primary endpoint of 90-day all-cause mortality (0.78% vs 0.73%, respectively)[2]. Furthermore, the incidence of pulmonary embolism (PE) was completely identical between the aspirin and LMWH cohorts at exactly 1.49%[2]. However, a distinct divergence occurred regarding local clots: the cumulative 90-day incidence of DVT was significantly higher in the aspirin group than the LMWH group (2.51% vs. 1.71%)[2]

Data regarding direct oral anticoagulants (DOACs), such as apixaban, takes a different clinical shape, relying on large observational registries and meta-analyses due to a lack of multi-center RCTs in acute trauma. The extensive National Trauma Quality Improvement Program (TQIP) registry study by Nederpelt et al[5] analyzed 4,560 propensity-matched patients with lower extremity fractures. They found that symptomatic VTE rates were completely identical at 1.4% for both the DOAC and LMWH cohorts, with a trend toward fewer bleeding interventions in the DOAC cohort (5.8% vs 6.0%)[5]. This therapeutic equivalence was reinforced by the systematic review and meta-analysis by Wu et al.[6], which concluded that DOACs carry an equivalent effect to LMWH in global VTE prevention (OR = 0.42, 95% CI [0.16–1.11]) while potentially showing minor superiority over LMWH in mitigating baseline DVT in lower limb injury cohorts.

National and regional guidelines contextualize these statistics for daily clinical protocols. Thrombosis Canada (2025)[7] guidelines accept the noninferiority of aspirin for mortality but explicitly warn that aspirin is less effective at suppressing nonfatal DVTs compared to LMWH. Meanwhile, trauma-focused panels, such as the Wisconsin TQIP Collaborative (2025)[8], maintain that LMWH should remain the hyperacute standard of care, initiated within 12–24 hours post-injury for high-risk open or complex extremity fractures, reserving oral alternatives for less severe injuries or post-discharge management.

Because LMWH is cleared by the kidneys, it accumulates in patients with severe renal impairment (creatinine clearance < 30 mL/min), drastically increasing major bleeding risk[4, 9]. Low-dose unfractionated heparin (UFH) relies on non-renal clearance mechanisms, rendering it the standard of care for trauma patients with acute kidney injury (AKI) or end-stage renal disease[9]. Furthermore, its rapid reversibility with protamine sulfate makes it highly suitable when an open fracture requires multiple immediate returns to the operating room for staged soft-tissue coverage or debridement.

Section 4: Discussion

The choice of thromboprophylaxis following high-energy orthopedic trauma, particularly open or complex fracture fixation, has seen a paradigm shift. Historically, clinical practice protocols heavily relied on injectable low-molecular-weight heparin (LMWH) due to its predictable pharmacokinetics and historical track record in suppressing the immense hypercoagulable state triggered by acute trauma. However, LMWH places notable burdens on the healthcare ecosystem, including high financial costs, patient aversion to subcutaneous injections, low post-discharge compliance, and risks of heparin-induced thrombocytopenia.

The publication of the PREVENT CLOT trial challenged the mandatory status of LMWH, definitively illustrating that low-dose oral aspirin is noninferior in preventing all-cause mortality and pulmonary embolism within 90 days of surgical fixation[2]. This provided an evidence-based pathway to utilize an incredibly inexpensive, universally accessible oral agent. Nonetheless, a critical clinical nuance remains: patients allocated to the aspirin group experienced a 47% relative increase in the rate of nonfatal deep-vein thrombosis (2.51% vs 1.71%)[2]. While these localized clots did not translate into fatal PE events within the trial window, the development of a DVT can lead to long-term post-thrombotic syndrome, chronic pain, and swelling, which delays physical rehabilitation in trauma patients. Consequently, many institutions remain reluctant to implement a blanket transition to aspirin, with contemporary trauma surveys showing that a substantial portion of orthopedic surgeons still prefer traditional LMWH for high-risk, high-energy open injuries[1]

This clinical hesitation is further supported by the demographic profile of the PREVENT CLOT cohort, where only 14% of the randomized population possessed an Injury Severity Score (ISS) greater than 15[1]. High-energy open fractures produce extensive periosteal stripping and soft-tissue destruction,[11] triggering a systemic hypercoagulable state through activation of the coagulation cascade and endothelial damage.[12] Prolonged immobilization further amplifies this prothrombotic milieu.[13] In this context, aspirin's antiplatelet mechanism—targeting thromboxane A2-mediated platelet aggregation—addresses only one arm of a multifactorial thrombotic process driven predominantly by thrombin generation and fibrinogen excess,[14] raising questions about its sufficiency as sole prophylaxis in this high-risk subgroup.[15]

Direct oral anticoagulants (DOACs), including apixaban, represent a compelling middle ground, combining the ease of oral administration with the targeted, potent mechanism of a factor Xa inhibitor. While DOACs are firmly established as a first-line option in elective total joint arthroplasties (where patients are optimized and stable), their utilization in acute trauma has historically been limited by a lack of prospective RCT data. However, the large-scale retrospective data from the National Trauma Quality Improvement Program (TQIP) provides robust real-world reassurance, demonstrating that trauma patients with lower extremity fractures experience identical symptomatic VTE rates (1.4%) whether they receive a DOAC or LMWH, alongside a comparable safety and bleeding profile[5]. The systematic review by Wu et al. (2025)[6] supports this, suggesting that DOACs provide adequate protective coverage that may match or slightly exceed LMWH for DVT reduction in lower extremity skeletal trauma.

Despite this positive real-world data, professional guidelines like the Wisconsin TQIP Collaborative (2025)[8] and Thrombosis Canada (2026)[7] maintain a cautious approach. They highlight that during the hyperacute phase of an open fracture (the first 24–48 hours), the risk of unpredictable surgical-site bleeding, haematoma formation, and the potential need for unplanned urgent return to the operating room for wound debridement make LMWH a safer short-term

choice. LMWH has a shorter half-life than DOACs and can be partially reversed if emergent surgery is required.

Crucially, when LMWH itself cannot be utilized due to acute kidney injury or severe chronic renal impairment, consensus guidelines mandate transitioning to low-dose unfractionated heparin (5,000 units TID) as the safest inpatient alternative due to its non-renal clearance and rapid reversibility[9]. This targeted utilization of low-dose heparin balances renal safety and bleeding control without exposing high-risk open fracture populations to the lesser anti-thrombotic efficacy of oral aspirin.

Therefore, while aspirin and apixaban represent highly viable, effective, and patient-friendly oral alternatives to LMWH, they are not completely interchangeable across all fracture phenotypes. LMWH remains highly favored during the acute inpatient phase for severe, complex open injuries and polytrauma, whereas aspirin and apixaban serve as excellent, highly effective agents for lower-risk isolated injuries or as extended step-down prophylaxis once a patient is stable and preparing for hospital discharge.

Section 5: Risk of Bias of Included Studies

- **O'Toole et al.[2] (PREVENT CLOT), 2023: LOW** risk of bias. It is a highly powered, multi-center, strictly randomized trial. Although it utilized an open-label design, all critical clinical endpoints were adjudicated by an independent committee completely masked to treatment allocation.
- **Nederpelt et al.[5], 2021: MODERATE** risk of bias. As an observational cohort study utilizing a national registry, it is inherently prone to historical confounding by indication. However, this risk was rigorously mitigated using a 1:1 propensity score matching model across a very large sample size ($N=4,560$).
- **Wu et al.[6], 2025: LOW to MODERATE** risk of bias. The systematic review methodology was sound, but it was limited by the small number of primary studies specific to trauma and lower limb fractures, as well as mild heterogeneity across the underlying patient cohorts.
- **Ley et al.[9] (Western Trauma Association), 2020: MODERATE** risk of bias. As a national clinical practice guideline and expert consensus decision algorithm, it relies heavily on the expert panel's interpretation of heterogeneous retrospective trauma literature; however, bias is minimized through structured, iterative consensus-building and strict adherence to established evidence-grading systems.

Section 6: Recommendation

It is acknowledged that there is no direct evidence regarding the quality of antithrombotic prophylaxis in open fractures. Consequently, the recommendation is based on studies related to trauma and fractures in general.

Oral aspirin (81 mg BID) and apixaban (or other DOACs) are effective oral alternatives to LMWH for preventing mortality and pulmonary embolism after fracture fixation. **However, we recommend LMWH as the preferred clinical standard during the hyperacute inpatient phase for complex open fractures and polytrauma** due to its superior reduction of nonfatal DVTs and more manageable bleeding profile if a return to the operating room is required. Furthermore, in patients with acute kidney injury or severe renal impairment (CrCl < 30 mL/min), low-dose unfractionated heparin (5,000 units TID) must be prioritized as the primary inpatient chemoprophylactic standard to avoid renal bioaccumulation and catastrophic bleeding.

Section 7: Level/Strength of Evidence

MODERATE

Justification: This protective recommendation is backed by **Moderate-Quality Evidence** consisting of clinical trial secondary endpoints, large-scale observational data, and expert national consensus guidelines.

- **DVT Efficacy Gap:** Trial data demonstrates that aspirin is associated with a significant 47% relative increase in nonfatal DVT rates (2.51\% vs. 1.71\%) compared to LMWH, rendering it less protective in high-risk, highly inflammatory open fracture environments.
- **Safety Profile:** Due to a lack of highly powered RCT data focusing specifically on open fracture populations for DOACs, national and regional guidelines (Thrombosis Canada, 2026; Wisconsin TQIP, 2025) provide strong consensus recommendations prioritizing LMWH during the first 12–24 hours post-injury. This is driven by its shorter half-life and partial reversibility, minimizing severe complications if an urgent return to the operating room for wound debridement or hematoma evacuation is required.

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