

Direct oral anticoagulants for venous thromboembolism prophylaxis in orthopaedic trauma: a clear first choice?

‘The brain may devise laws for the blood’

William Shakespeare, *Merchant of Venice* (1598)¹

Prevention of venous thromboembolism (VTE) is an integral part in the care of orthopaedic patients. VTE the leading cause of preventable mortality in hospital² and orthopaedic surgery confers particularly high-risk.³ VTE currently complicates 2%–7% of all orthopaedic surgery.² Symptomatic VTE results in reduced quality of life and causes mortality in 6%–12% of cases.⁴ VTE may increase length of stay (LOS) in hospital and confers large economic costs.⁵

Biological rationale supports the efficacy of direct oral anticoagulants (DOACs) for VTEp in orthopaedic surgery. Orthopaedic surgery accentuates all aspects of Virchow’s Triad due to trauma-induced thromboplastin upregulation, intraoperative tourniquet use, immobilization, bed rest and polymethylmethacrylate cement.⁶ DOACs prevent subsequent coagulation by inhibiting Factor Xa or II.⁶ Factor Xa inactivation is also the mechanism of action for low-molecular-weight heparins (LMWH) which are commonly used for VTEp after orthopaedic surgery.³ However, DOACs act directly on coagulation factors, unlike LMWH which is reliant on the presence of antithrombin III. DOACs do not require dose adjustment in obesity and avoid the gastrointestinal and renal side-effects of aspirin. The disadvantage of DOACs is that they are not all reversible and have a longer washout time than LMWH.

DOACs have already demonstrated utility for VTEp in alternative domains. Most notably, DOACs are now suitable first-line options for VTEp after hip and knee arthroplasty. LMWHs such as enoxaparin, had historically been the gold-standard for VTEp after arthroplasty.⁷ However rivaroxaban and apixaban have demonstrated superior VTEp than LMWH in recent meta-analyses of randomized controlled trials (RCT).^{8,9} Rivaroxaban was associated with a greater bleeding risk than LMWH.^{8,9} This is important to note as, even minor bleeding is a concern to orthopaedic surgeons as it may increase risk of infection. However, apixaban has demonstrated a lesser bleeding risk than LMWH.^{8,9} Meanwhile, aspirin has shown significantly increased VTE and mortality rates when compared to DOACs and LMWH.^{10,11} Apixaban and rivaroxaban have also demonstrated reduced rates of symptomatic VTE than LMWH without increased incidences of major bleeding, when used for VTEp in oncology.¹²

Studies from the last decade have consistently demonstrated the benefits of DOACs over LMWH for VTEp in orthopaedic trauma surgery.^{13,14} A recent systematic review and meta-

analysis reported significantly reduced deep venous thrombosis rates when Factor Xa inhibiting DOACs were compared to LMWH for VTEp after lower limb fracture surgery.¹⁴ DOACs were also not inferior to LMWH for prevention of mortality, pulmonary embolism and bleeding, both major and minor. A RCT not included in the aforementioned study demonstrated reduced VTE risk with no increase bleeding risk, including minor bleeding, when rivaroxaban was compared to LMWH.¹³ Therefore the increased bleeding with rivaroxaban in some arthroplasty data is not reflected in orthopaedic trauma. Aspirin has not demonstrated effective VTEp after orthopaedic trauma surgery when compared to LMWH.¹⁵ The results of these studies have not yet effected an update to international guidelines for VTEp after orthopaedic trauma surgery (Table 1).

DOACs also offer large economic savings, superior patient experience and improved adherence when compared to LMWH. In analyses for total hip replacement and total knee replacement, dabigatran, rivaroxaban and apixaban demonstrate saving of €152 and €116, €177 and €85, €223 and €135 per patient respectively.⁵ DOACs are administered orally compared to LMWH administration by subcutaneous injection. LMWH has subsequently been associated with high rates of non-adherence after hospital discharge.¹⁶ This is particularly concerning as the majority of VTE occurs following hospital discharge.¹⁷

Evidence suggests DOACs are the first choice over LMWH for VTEp after orthopaedic trauma surgery due to reduced rates of VTE, equivocal bleeding risk and mortality, reduced cost and improved patient experience. Where bleeding risk is high, apixaban may be used instead of rivaroxaban. Where risk of reoperation is high, DOACs should be avoided as they are not reversible.

Table 1 A summary of current guidelines for VTEp after orthopaedic surgery

Guidelines	Arthroplasty	Orthopaedic trauma surgery
European	No published orthopaedic guidelines	No published orthopaedic guidelines
Eastern Association for Surgery of Trauma ¹⁸	Enoxaparin or Dalteparin (LMWH)	Enoxaparin (LMWH)
Asia-Pacific ¹⁶	DOACs, aspirin or LMWH	DOACs, aspirin or LMWH (Hip fracture fixation only)

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