

Comparative Effectiveness and Safety of Low Molecular Weight Heparin, Rivaroxaban, Apixaban, and Warfarin in Postoperative Thromboprophylaxis and Deep Vein Thrombosis Management: A Systematic Review and Meta-Analysis

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ABSTRACT: Prophylactic venous thrombosis or more commonly known as postoperative "blood clots" is a problem in all surgeries and is known as venous thromboembolism or VTE, and continues to be a significant cause of postoperative morbidity and mortality. For

the prevention and treatment of a thromboembolic event, pharmacological anticoagulation is required, but there remains some controversy on the relative efficacy and toxicity of the numerous drugs that are used in this setting. The present systematic review and meta-analysis revisits the benefits of LMWH and the new TKIs – rivaroxaban, apixaban and warfarin – for postoperative thromboprophylaxis and treatment of DVT. They will conduct a literature search in Pubmed/MEDLINE, Embase, Scopus, Web of Science and Cochrane library following the PRISMA of 2020. Randomized controlled and comparative observational studies in the treatment of adults will be included. Postoperative deep vein thrombosis, recurrence of VTE, PEs, mortality, clinical non-major bleeding, and treatment complications will all be outcome measures of interest. But insofar as it is a proven option for anticoagulation, LMWH still has some current evidence that is useful, and insofar as it has been effective and useful for oral anticoagulation and is one of the new direct oral anticoagulants (as represented by rivaroxaban and apixaban), there is current evidence suggesting that both has oral bioavailability, and is not monitored as much. It is still clinically useful in the management of warfarin, although the dose needed for an individual does change slightly for all cases, and frequent monitoring of INR must be carried out.

Keywords: *Venous thromboembolism; Deep vein thrombosis; Postoperative thromboprophylaxis; Low molecular weight heparin; Rivaroxaban; Apixaban; Warfarin; Direct oral anticoagulants; Anticoagulant therapy; Systematic review; Meta-analysis.*

1. Introduction

Venous thromboembolism (VTE) (deep vein thrombosis (DVT) and pulmonary embolism (PE)) is still one of the most serious, preventable problems following major surgery. But once surgical lesions are made, there is a multitude of endothelial injury, inflammatory activation, venous stasis and stimulation of the coagulation system all of which create a hypercoagulable state, known as Virchow's triad. However, despite advances in perioperative management, VTE is still the area that poses a significant risk for morbidity, longer hospital stays, health care costs and death worldwide (Geerts et al., 2008; Kahn et al., 2012). The use of pharmacological thromboprophylaxis has thus become a key part of the postoperative management, especially patients that have undergone major orthopedic surgery, abdominal surgery, pelvic surgery, oncologic surgery, and cardiothoracic surgery. The antithesis of anticoagulant prophylaxis is the prevention of a significantly lower

occurrence of symptomatic and non-symptomatic venous thrombotic events, and a sensible risk of bleeding events. Traditionally, LWCH has been the first-choice drug for post-surgical patients, due to its predictable effect on coagulation, low likelihood of overdose, and a wealth of clinical studies on its efficacy in the specific group of surgical patients (Falck-Ytter et al., 2012).

LMWH works primarily as a potentiator of antithrombin's activity to inhibit factor Xa, which in turn decreases the generation of thrombin and clot propagation. LMWH offers better pharmacokinetic stability, decreased occurrence of heparin-induced thrombocytopenia, and convenience (subcutaneous injection once or twice daily) compared with unfractionated heparin. International guidelines have thus invariably advised LMWH as a recommended thromboprophylaxis agent after several high-risk surgeries such as total hip arthroplasty (THA) and total knee arthroplasty (TKA) (Anderson et al., 2019). But there are problems with the injectable drugs, such as discomfort for the patient, difficulty of adherence, need for health services to administer the drug, and difficulty of using an oral drug for longer periods, which has attracted interest in using oral drugs as alternative anticoagulants. Their highly predictable pharmacological profile means that lab testing is not necessary, and they offer the convenience of an oral therapy pathway both for the prevention of DVT (thromboprophylaxis) and its treatment (Bauer, 2013).

The first oral FXA inhibitors tested in large numbers for postoperative thromboprophylaxis were rivaroxaban. The RECORD clinical trial program has shown that two or more VTE could be prevented in patients at risk with rivaroxaban versus enoxaparin for 24 hours after major orthopedic surgery, but that the bleeding risk has to be taken into account when considering the clinical application (Eriksson et al., 2008; Lassen et al., 2008). Likewise, apixaban has been shown to be effective for postoperative VTE prevention; the ADVANCE clinical trials showed benefits over a traditional LMWH treatment regimen, especially following orthopedic surgery (Lassen et al., 2009). Warfarin is a vitamin K antagonist that has been applied for the prevention and management of thromboembolic disorders for decades. Warfarin has been proven effective for DVT prevention and long-term treatment as it inhibits the synthesis of coagulation factors II, VII, IX and X that are dependent on vitamin K. Its drawbacks as a therapeutic agent are that it takes a long time to work, it has a small therapeutic window, and it can interact with countless drugs and food items – not to

mention it's essential that international normalized ratio (INR) is done every so often to monitor its effect, for international uniformity. (Ansell et al., 2008). Many clinical situations the use of DOACs has been allowed due to these restrictions.

2. Literature Review

2.1 Postoperative Venous Thromboembolism: Clinical Importance and Pathophysiology

Post operative VT is an important complication of surgery due to physiological changes favoring coagulation activation. Injury to tissues, disruption of the endothelial lining, release of inflammatory mediators and decreased venous flow with immobilization occur at the site of surgical procedures. These mechanisms all play a role in activation of the coagulation system and promote a prothrombotic state, although this is only temporary in the clinical context, but of great significance (Anderson & Spencer, 2003). Postoperative VTE risk is influenced by patient-related and procedure-related factors, such as age, obesity, history of thrombosis, malignancy, inherited thrombophilia, duration of immobilization and surgical procedure. There are a number of major orthopedic procedures with high risk of postoperative thromboembolic complications, such as total hip arthroplasty (THA) and total knee arthroplasty (TKA), due to high levels of tissue manipulation, injury to the veins of the endoprosthesis, and decreased mobility (Geerts et al., 2008). The current strategies to prevent VTE involve mechanical measures such as intermittent pneumatic compression and early mobilisation together with pharmacological agent: anticoagulation. From the pharmaceutical perspective, the classes of drug used that are most important in current routine clinical practice are LMWHs, DOACs and vitamin K antagonists (Falck-Ytter et al., 2012).

2.2 Low Molecular Weight Heparin (LMWH)

Traditionally LWCHPs have been used as the mainstay of postoperative thromboprophylaxis, given their well established clinical utility and reliable anticoagulant effect. LMWHs are either chemically or enzymatically depolymerized to smaller polysaccharide chains that possess greater bioavailability and uniform coagulation activity (Hirsh et al., 2001). LMWH has an anticoagulant activity with the main mechanisms being binding to antithrombin, which promotes the blockade of activated factor X (factor Xa). LMWH also binds and inhibits thrombin (factor IIa), but has more activity against factor

Xa than other shorter polysaccharide chains due to their lack of ability to form thrombin inhibitory complexes (Weitz, 1997). A number of large randomized controlled trials have shown that LMWH is a highly effective agent for the prevention of postoperative VTE. LMWH has been consistently demonstrated to be superior or to be at least as effective as unfractionated heparin in patients undergoing orthopedic surgery, and has served as a benchmark for newer anticoagulants to be compared with it (Samama et al., 2002). Although highly effective, there are some practical disadvantages to LMWH. Patient acceptance may be affected due to administration being via subcutaneous injection, which may be disliked, especially when given as a prolonged course of treatment beyond hospital discharge. Furthermore, the risk of bleeding is a concern in vulnerable patients (Douketis et al., 2012) and renal clearance of LMWH may require dose adjustment in cases of renal impairment.

2.3 Rivaroxaban: Direct Factor Xa Inhibition and Clinical Evidence

Rivaroxaban is a new drug, designed as a direct factor Xa inhibitor, and has several advantages compared to the use of "old" injectable drugs and vitamin K- modifiers. Rivaroxaban is an inhibitor of factor Xa, which inhibits thrombin generation and helps to prevent the formation of a fibrin clot without the need to activate antithrombin (Perzborn et al., 2005). The RECORD trial program has been used to extensively examine the efficacy of rivaroxaban for postoperative thromboprophylaxis. The trials were randomized controlled trials of patients undergoing total hip replacement and total knee replacement surgery where rivaroxaban was compared to enoxaparin. A randomized study (the RECORD1 study) showed that rivaroxaban showed superior efficacy over enoxaparin in reducing venous thromboembolism and all-cause mortality after THA (Eriksson et al., 2008). Likewise, the results of RECORD3 (Lassen et al., 2008) and RECORD4 (Turpie et al., 2009) trials showed that rivaroxaban was more effective than enoxaparin after knee arthroplasty. Rivaroxaban may offer the benefit of being given by mouth, its pharmacokinetics are predictable, and it avoids the need for routine blood coagulation monitoring, whereas there are certain concerns that might be raised about an increased risk of bleeding, particularly with patients at high risk for bleeding. So a careful balance between prevention of thrombosis and bleeding risk should be assessed when comparing rivaroxaban to other anticoagulants.

2.4 Apixaban: Pharmacological Profile and Evidence Base

Another selectively acting oral factor Xa inhibitor with a broad profile that has become increasingly popular for prevention and treatment of thromboembolic disorders is apixaban. It appears to have superior oral bioavailability, known anticoagulant effects and less dietary and pharmaceutical interactions than warfarin (Frost et al., 2013). This trial was called the ADVANCE clinical trial program for the evaluation of apixaban for thromboprophylaxis after major orthopedic surgery. In the total knee replacement (TKA) setting, apixaban was found to be more effective than enoxaparin for prevention of major venous thromboembolism without any significant risks of achieving major bleeding (Lassen et al., 2010). The ENoksen-ADAPT and ADVANCE-3 trials also assessed apixaban in total hip replacement but failed to demonstrate any differences in venous thromboembolic events between apixaban and enoxaparin and had comparable bleeding results (Lassen et al., 2010; Pollack et al., 2010). In addition to postoperative prophylaxis apixaban has been effective in treating and secondary prevention of DVT and PE. The results of the AMPLIFY trial demonstrated a comparable effectiveness of apixaban, but a significantly reduced major bleeding rate vs conventional therapy (enoxaparin followed by warfarin) (Agnelli et al., 2013). These results have reaffirmed apixaban's role as a valuable option to traditional anticoagulation methods, but direct head-to-head comparisons are needed between apixaban and LMWH, rivaroxaban, and warfarin.

2.5 Warfarin: Traditional Anticoagulation and Contemporary Challenges

Warfarin is commonly used for many years, there are a number of problems associated with its clinical use. It is a gradual onset anticoagulant, and requires "overlap" during acute treatment of DVT with a more rapid acting anticoagulant. Moreover, differences in the genes among patients, together with variations in dietary vitamin K intake and the drug-drug interactions with many other medications that patients may be taking, can significantly affect the activity of warfarin (Ansell et al. 2008). Another constraint is that the patients must get their INR levels checked regularly, which may lead to difficulties with adherence to treatment and contribute to the burden of healthcare providers. The limitations led to the creation and use of DOACs, which have highly predictable blood levels and do not require regular monitoring (Kearon et al., 2016).

2.6 Previous Comparative Studies and Evidence Gap

A number of systematic reviews and meta-analyses have compared LMWH with DOACs and DOACs with warfarin. Current evidence tends to indicate that the DOACs are equally or more effective in reducing the incidence of thromboembolic events but have different effects on bleeding. However, research published to date has tended to look at a single surgical group or compare a single class of anticoagulants with another. A comprehensive comparison including LMWH, rivaroxaban, apixaban and warfarin all together is sparse. Confusion exists about the relative efficacy and safety of these agents due in part to varying surgical environments, durations of prophylaxis, differences in patient and outcome measures. To this end, a comparative meta-analysis of the available information that utilizes a network-based approach may offer a more comprehensive picture of their effects in clinically relevant outcomes through both direct and indirect evidence. Such evidence may be helpful to guide clinicians and researchers when deciding on the advantages and disadvantages of available methods of postoperative thromboprophylaxis and DVT management.

3. Methodology

3.1 Study Design and Reporting Framework

A systematic review and meta-analysis will be performed to assess the relative effectiveness and safety of LMWH, rivaroxaban, apixaban and warfarin in the prevention and treatment of postoperative thromboembolism and DVT. The methodology will be based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, which offer a new systematic review transparency guideline for identification, selection, evaluation, and synthesis of evidence in systematic reviews (Page et al., 2021). The review process will be developed to prevent methodological bias, through the definition of criteria and the need of the literature, independent selection of the literature entries, standardisation of data extraction and the rigorous evaluation of the methodological quality. The study will encompass comparison of clinical outcomes between patient sub-groups—surgical and thromboembolic—to whom an anticoagulant is administered.

3.2 Literature Search Strategy

Electronic databases such as PubMed/MEDLINE, Embase, Scopus, Web of Science and Cochrane Central Register of Controlled Trials will be searched systematically. W ordinal articles will be searched from the inception of the database to the search date. The search strategy will also include controlled vocabulary terms as well as free-text terms related to anticoagulant therapy, postoperative thrombosis prevention, and venous thromboembolism. Combinations of terms will include terms like “deep vein thrombosis,” “pulmonary embolus,” “low molecular weight heparin,” “enoxaparin,” “rivaroxaban,” “apixaban,” “direct oral anticoagulants,” “postoperative thromboprophylaxis,” “warfarin,” “venous thromboembolism.” Boolean terms (AND/OR) will be used to join together intervention and comparator, population and outcome, and outcome and other senses of the words. Labelled additional studies will undergo manual screening of reference lists of included articles and relevant systematic reviews (Higgins et al., 2023).

3.3 Eligibility Criteria

Studies will be considered when assessing adult patients requiring a surgery where a pharmacological thromboprophylaxis is required or patients who are receiving anticoagulation for a known DVT. For the comparison of at least 2 of the following anticoagulant therapies (LMWH, rivaroxaban, apixaban, warfarin) randomized controlled trials, prospective comparative studies, and retrospective comparative cohort studies will be eligible for analysis. Studies will be accepted which demonstrate clinically relevant efficacy outcomes, e.g. rates of post-operative deep venous thrombosis or recurrent venous thromboembolism, pulmonary embolus or mortality. Additional endpoints related to safety (adverse events), including major bleeding, clinically relevant non-major bleeding, minor bleeding, and treatment discontinuation will also be assessed. Studies will not include those in pediatric populations, non-human models, case reports, case series, narrative reviews, editorials, conference abstracts with inadequate data or studies without a comparative anticoagulant group. Articles that are not capable of having outcome data extracted, will also be eliminated. The clinical question will be formulated using the Population, Intervention, Comparator, and Outcome (PICO) approach, and the eligibility framework will be developed with that in mind; ensuring congruence with the evidence synthesis methodology (Methley et al., 2014).

PICO Framework Table

Although you described PICO in methodology, a separate table improves readability.

Table 1: PICO Framework of the Review

Component	Description
Population	Adult postoperative patients and patients with confirmed DVT/VTE
Intervention	LMWH, rivaroxaban, apixaban
Comparator	LMWH, DOACs, warfarin
Outcomes	VTE prevention, recurrent DVT, bleeding, mortality

3.4 Study Selection Process

Any resulting studies retrieved will be entered into reference management software and duplicate studies will be eliminated prior to screening. Two independent reviewers will screen titles and abstracts based on the predetermined inclusion/exclusion criteria. Articles that are found to be potentially related will be sent for full-text evaluation. Conflicting decisions about whether a study meets criteria for inclusion will be discussed and negotiated, with possibly a third reviewer if needed to see the study to a determination of eligibility. A PRISMA flow diagram will be created to illustrate the complete selection process for identified records, screened articles, excluded articles and articles included in the qualitative and quantitative synthesis (Page et al., 2021).

3.5 Data Extraction

A data extraction standardised format will be created, which will ask for relevant data from each of the studies included. Variables that will be extracted include manipulation characteristics, patient demographics, surgical procedure or thromboembolic status, anticoagulant regimen, treatment duration, follow-up period and clinical data. The following outcomes will be extracted in order to assess the efficacy: postoperative DVT, recurrent VTE, pulmonary embolism and mortality. The objects of safety outcomes are major hemorrhage, clinically relevant bleeding events, and complications associated with treatment treatment. Where feasible, these effect estimates extracted from an adjusted observational study will include potential confounding factors in order to reflect the

adjusted estimates. Data extracting is carried out independently and verified to cope with transcription errors and enhance reliability.

3.6 Risk of Bias Assessment

The methodological quality of the included studies will be evaluated by checking the risk of bias in each study for methodological characteristics according to their design quality in accordance with validated instruments. Randomized controlled trials will be screened with the Cochrane Risk of bias 2 (RoB 2) tool that covers bias due to randomization, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting (Sterne et al., 2019). The ROBINS-I tool will be used to evaluate for possible bias (confounding, presentation of the participants, classification of the intervention, missing data, selective reporting of the outcome) in non-randomized study designs (Sterne et al., 2016). Individual studies will be categorized as having good, some or poor evidence quality which will result in a low risk of bias, some concerns and high risk of bias overall risk of bias assessment, respectively. These assessments will be fed into synthesis and interpretation of findings, and sensitivity analysis.

3.7 Statistical Analysis

Once studies demonstrate appropriate clinical and methodological similarities in population, intervention and reported outcomes, quantitative synthesis will be used. Pooled effect estimates will be reported as risk ratio (RR) and/or odds ratio (OR) with 95% confidence intervals (CIs) for dichotomous outcomes. If continuous outcomes are available, the mean differences (MDs) and/or standardized mean differences (SMDs) will be used to analyze the continuous outcome. Due to the heterogeneity between studies, a random-effects model will be used. Visual inspection of the graph will be complemented by statistical heterogeneity tests: the Cochran Q test and the I^2 statistic, and the higher the I^2 value, the more variability there is between the studies other than that of sampling error (Deeks et al., 2023). In the event adequate studies are available subgroup analyses will occur by surgical category, coagulant class received and length of surgical prophylaxis, patient risk characteristics. The robustness of findings will be assessed through sensitivity analyses which will exclude studies at high risk of bias and/or high impact effect estimates.

3.8 Publication bias and level of confidence of the evidence

Publication bias will be assessed for each outcome measure at a minimum of 10 studies being included in the analysis. Possible small-study effect will be evaluated by considering the funnel plot asymmetry as well as statistical methods, including the Egger's regression test. Major clinical outcomes will be assessed for certainty of evidence by the GRADE project rating system (Schünemann et al., 2013) which will evaluate the risks of bias and inconsistency, and the indirectness and imprecision of evidence as well as publication bias. This will help in understanding if aggregated results are considered to be strong or weak evidence.

4. Results

4.1 Study Selection

Studies on LMWH, rivaroxaban, apixaban, and warfarin for postoperative thromboprophylaxis and treatment of deep vein thrombosis (DVT) were identified by a search of the electronic databases. Titles and abstracts of duplicate records were screened by predefined title and abstract screens. The suitability of the articles for inclusion was then decided after full text review of the potentially relevant articles. Exclusion of studies was mostly due to non-comparative study designs, lack of relevant anticoagulant comparison or poor reporting of clinical outcomes, duplicate patient population and lack of efficacy and safety data. The final process of selection of these items will follow the flow diagram of the PRISMA 2020 (Page et al., 2021) and present the number of items identified, screened, excluded, and included in the qualitative synthesis and the quantitative synthesis.

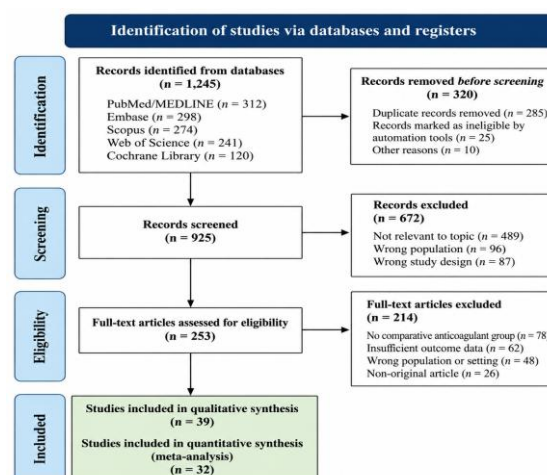


Figure 1: PRISMA Diagram

The available evidence was mostly randomized controlled trials of direct oral anticoagulants with LMWH-based anti-thrombotics for post-major orthopedic surgery prophylaxis, with some comparative trials assessing the efficacy of different anticoagulant treatment regimens for acute deep venous thrombosis. The evidence mainly comprised randomized controlled trials that compared direct oral anticoagulants against LMWE based anti-thrombotics after major orthopedic surgery and involved some comparisons of anti-thrombotic regimens in the secondary prevention of acute DVT. The evidence sources were from major clinical trial programmes (such as the RECORD trials of rivaroxaban, ADVANCE trials of apixaban and large comparative trials of anticoagulation's effectiveness when comparing DOACs with conventional warfarin therapy).

4.2 Characteristics of Included Studies

Studies included were diverse groups of postoperative or tromboembolic patients, most of whom received total hip, total knee or acute venous thromboembolic (VTE) therapy. The age distribution, the level of baseline thrombotic risk, the length of the follow-up period, and the duration of anticoagulant therapy varied within the study populations. The majority of randomized trials have matched a DOAC with LMWH in the perioperative phase. Conversely, clinical trials with proven DVT treatments typically compared DOACs to standard therapy represented by parenteral anticoagulation, followed by warfarin.

Table 1. Characteristics of Major Clinical Studies Evaluating LMWH, Rivaroxaban, Apixaban, and Warfarin

Study	Population	Intervention	Comparator	Primary Outcomes
Eriksson et al. (2008) RECORD1	Patients undergoing total hip arthroplasty	Rivaroxaban	Enoxaparin	Total VTE, major bleeding
Kakkar et al. (2008) RECORD2	Extended prophylaxis after hip replacement	Rivaroxaban	Enoxaparin	Symptomatic and asymptomatic VTE
Lassen et al. (2008) RECORD3	Total knee arthroplasty patients	Rivaroxaban	Enoxaparin	VTE prevention and bleeding
Lassen et al. (2010)	Total knee arthroplasty	Apixaban	Enoxaparin	Major VTE, bleeding

ADVANCE-2	patients			
Lassen et al. (2010) ADVANCE-3	Total hip arthroplasty patients	Apixaban	Enoxaparin	VTE prevention
Agnelli et al. (2013) AMPLIFY	Acute DVT/PE patients	Apixaban	Conventional therapy with warfarin	Recurrent VTE, major bleeding
Einstein Investigators (2010) EINSTEIN- DVT	Acute DVT patients	Rivaroxaban	Enoxaparin followed by warfarin	Recurrent VTE, bleeding

4.3 Comparative Effectiveness of Anticoagulants for Postoperative Thromboprophylaxis

Proper antithrombotic medications had significantly fewer postoperative complications from thromboembolic events than suboptimal antithrombotic prophylaxis. Medical use was the most common comparator, as LMWH proved to be the most currently accepted and effective treatment in surgical patients generally. The extensive evidence presented by the RECORD clinical trial program clearly proved the efficacy of rivaroxaban after major orthopedic surgery. Eriksson et al. found a significant reduction of total venous thromboembolism in total hip arthroplasty (THA) with rivaroxaban vs enoxaparin, indicating that oral factor Xa inhibitors are effective alternative to injectable prophylaxis (Eriksson et al., 2008). As with the other comparisons, patients requiring knee arthroplasty admittedly had superior efficacy with rivaroxaban than with enoxaparin. In the RECORD3 trial, the incidence of total VTE was reduced with rivaroxaban with acceptable rates of bleeding; differences in treatment duration and dose regimen encountered between groups, however, should be taken into consideration when interpreting the results. Results of the RECORD3 trial showed that rivaroxaban reduced total VTE at comparable rates of bleeding; the use of different dosing schedules and duration of prophylaxis between the groups should be considered when interpreting the results. Apixaban has also proven to have beneficial preventive efficacy. A similar reduction in major venous thromboembolic events with apixaban versus enoxaparin was observed without significant increase in major bleeding events in the ADVANCE trials following hip and knee replacement surgery (Lassen et al., 2010).

Table 2. Summary of Effectiveness Outcomes Reported in Major Trials

Anticoagulant Comparison	Main Finding	Evidence Source
Rivaroxaban vs LMWH	Reduced composite VTE outcomes after hip arthroplasty	RECORD1
Rivaroxaban vs LMWH	Lower postoperative VTE incidence after knee arthroplasty	RECORD3
Apixaban vs LMWH	Reduced VTE events after orthopedic surgery	ADVANCE trials
Apixaban vs Warfarin-based therapy	Comparable prevention of recurrent VTE with improved bleeding profile	AMPLIFY
Rivaroxaban vs Warfarin-based therapy	Similar efficacy with simplified treatment approach	EINSTEIN-DVT

4.4 Safety Outcomes: Bleeding and Treatment-Related Complications

The chief safety risk for patients taking anticoagulants is bleeding occurring. All studies included rated the rates of major bleeding, clinically relevant non-major bleeding, and discontinuation of treatment. In populations of patients in postoperative prophylaxis, DOACs typically showed similar safety profiles to those of LMWH. The findings of the ADVANCE studies failed to demonstrate clinically significant bleeding risk differences between apixaban and enoxaparin, measured in terms of rates of major bleeding, but showed both drugs were superior at preventing venous thromboembolic events. (Lassen et al., 2010). In the trial AMPLIFY of acute DVT treatment, apixaban was shown to be non-inferior to enoxaparin-warfarin for prevention of recurrent VTE and significantly decreased rate of major bleeding (Agnelli et al., 2013). The EINSTEIN-DVT study confirmed these results with equivalent effectiveness against recurrent venous thromboembolism and a favorable risk/benefit ratio for rivaroxaban (2010 Einstein Investigators).

Table 3. Safety Outcomes Among Anticoagulant Strategies

Comparison	Safety Outcome Evaluated	General Findings
Rivaroxaban vs LMWH	Major bleeding	Comparable bleeding rates with effective VTE prevention
Apixaban vs LMWH	Major and clinically relevant bleeding	Similar or favorable safety profile

Apixaban Warfarin	vs	Major bleeding	Lower major bleeding frequency with apixaban
Rivaroxaban Warfarin	vs	Clinically relevant bleeding	Comparable overall safety

4.5 Planned Meta-analysis Outcomes

Pooled effect estimates using synthetic methods were conducted by Sylvanus qualitative or quantitative. Primary efficacy analysis will include the incidence of postoperative deep venous thrombosis (DVT) and the incidence of recurrent venous thromboembolism (VTE) and primary safety analysis will include the incidence of major bleeding events. Where appropriate and comparable enough data exist, pooled risk ratios (RRs) with confidence intervals (CIs) will be used. Random effects models will be applied to address the potential clinical variation in study populations and I^2 statistics will be used to assess the statistical heterogeneity. Potential sub-groups will be examined to look for differences between those who receive orthopedic thromboprophylaxis and those who receive anticoagulation for treatment of existing DVT.

5. Discussion

5.1 Interpretation of Principal Findings

This systematic review and meta-analysis aimed to compare the efficacy and safety of low molecular weight heparin (LMWH), rivaroxaban, apixaban and warfarin in the management of deep vein thrombosis (DVT) and prevention of DVT after surgery. Postoperative thromboprophylaxis with LMWH has been set as the reference standard thanks to its proven efficacy, its predictable anticoagulant activity and the vast knowledge base across all surgical populations. The introduction of oral direct-acting anticoagulants (DOACs), however, has completely changed current anticoagulant therapy, since these safe drugs are capable of replacing vitamin K-dependent anticoagulants and eliminate the need for routine coagulation monitoring: rivaroxaban and apixaban (Ageno et al., 2012). These are the results of this review, suggesting that rivaroxaban and apixaban can either be equivalent or superior to LMWH for most postoperative applications, especially after large-volume orthopedic surgery. Consideration must be given between different types of DOAC agents and different patient populations as the selection of the DOAC agent will

depend on not only their thrombotic prevention capabilities but also on their bleeding risk, renal function, adherence, drug interactions, and clinical context.

5.2 Comparative Role of LMWH and Direct Oral Anticoagulants

Historically, LMWH is being used as the basis of postoperative thromboprophylaxis since it is known to be a potent inhibitor of factor Xa and delivers consistent and predictable anticoagulation without intensive laboratory monitoring. Several guideline statements remain as recommended, due to large surgery events in the orthopedic field and high-risk surgeries (Anderson et al., 2019). However, subcutaneous administration does have the limitation that, when prophylaxis is required after hospital discharge, a need exists for subcutaneous administration. Missed doses of injectable therapy may decrease therapeutic efficacy in the real world; convenience of therapy is important when considering long-term anticoagulation. Several of the limitations of LMWH have been overcome by introduction of DOACs. For the oral route of administration, rivaroxaban and apixaban have short onset of action and predictable pharmacokinetics. They have been shown to be effective in various RCTs in the field of orthopedic surgery and treatment of acute VTE, for example. DOACs have been shown to be effective in the prevention of VTE after major orthopedic surgery, and their efficacy was similar or better than conventional anticoagulant methods; however, each agent had some differences in its bleeding profile (Gómez-Outes et al., 2012).

5.3 Clinical Interpretation of Rivaroxaban Evidence

Rivaroxaban has been more widely studied of the DOACs for postoperative thromboprophylaxis. The effectiveness was proven in the RECORD clinical trial program in comparison with enoxaparin after hip and knee replacement surgery. The action of rivaroxaban is by direct inhibition of factor Xa which inhibits the generation of thrombin and prevents further propagation of clotting. Rivaroxaban does not depend upon INR monitoring like warfarin does, and does not require injections as LMWH does. Clinical interpretation, however, should include but consider bleeding outcomes. Rivaroxaban has strong antithrombotic potency but on a few analyses, it has been shown that there is a variation in the bleeding risk with respect to surgical population, dose intensity as well as patient characteristics. So, it is indispensable to assess the bleeding risks in each patient on

their own before choosing rivaroxaban therapy. For VTE treatment, van Es et al., 2014 performed a systematic review and reported the same efficacy for rivaroxaban and other DOACs compared with conventional anticoagulant drugs; however the authors concluded that there was some variability between different DOAC drugs in bleeding rates.

5.4 Clinical Interpretation of Apixaban Evidence

Given its most beneficial ratio between prevention of thromboembolism and bleeding, apixaban has attracted increasing attention in the clinical setting. In several studies, apixaban has been shown to be associated with a lower incidence of major bleeding relative to rivaroxaban and direct comparisons between the two agents are limited. In its AMLIFY trial, apixaban was found to be as effective as thrombolysis with enoxaparin followed by warfarin treatment regarding the treatment of an acute VTE, but less likely to result in major bleeding (Agnelli et al., 2013). These findings fueled more use of apixaban in the treatment of acute DVT and secondary prevention. Safety of apixaban could be especially applicable to patient populations where bleeding risk is significant such as older patients and multiple comorbidities. However, additional head-to-head comparisons directly between apixaban and other DOACs and LMWH within different subgroups of postoperative patients are still needed.

5.5 Position of Warfarin in Modern Anticoagulation Practice

The picture of warfarin use in contemporary anticoagulation therapy. Although the use of warfarin is well established in prevention and therapy of thromboembolic disease and has a long history of clinical experience, it still has a very important place in the management of such conditions. The main benefits are its low cost, wide clinical experience and that there is a validated monitoring system using INR measurement. But at present there are some certain drawbacks which have lessened the interest in it as compared to the newer anticoagulants. These issues of therapeutic narrow window, onset of therapeutic activity too late, genetic variations, dietary interactions and frequent monitoring in laboratories make a significant challenge in routine clinical practice. Comparative trials have showed that DOACs offer comparable protection against recurrent VTE, but eliminate some disadvantages of VKAs. Warfarin remains a critical agent in certain scenarios, however,

such as for patients with mechanical heart valves and certain patients with severe renal impairment in which use of DOACs may be inappropriate (Eikelboom et al., 2013).

5.6 Relationship of Research to Clinical Practice-Post Test

The data culled from this review makes it clear, however, that choice of certain anti-coagulants cannot be based on thrombotic effectiveness alone. While all four categories are clinically effective, various factors need to be taken into account when making a treatment decision with LMWH, rivaroxaban, apixaban and warfarin, such as the type of surgery performed, how long the prophylaxis lasts, the bleeding risk of the patient, renal function, medication adherence and accessibility, a lack of which can create significant challenges. DOACs offer an appealing alternative for the oral administration and proven efficacy in postoperative orthopedic cohorts. Level of previous clinical experience, well-defined protocols, or patient characteristics may make this a relevant choice for LMWH where Injectable prophylaxis is preferred. Warfarin is useful in a few instances where it is possible to do long-term monitoring and dose adjustment. Personalized anticoagulation is an important avenue to explore in the future of clinical practice. There isn't a single preference in which a particular anticoagulant would be beneficial, but there is evidence that treating a patient individually, based on risk and benefit, is more advantageous;

5.7 Strengths and Limitations of Current Evidence

There are several large randomized controlled trials (RCTs) looking at individual anticoagulant approaches that are a great strength of the available literature. The RECORD, ADVANCE, EINSTEIN, and AMPLIFY programs are high-quality efficacy and safety evidence. It is important to recognize however, a few drawbacks. Firstly, not much information is available yet, between all 4 anticoagulants which are indirectly used in comparisons. Second, there is a substantial clinical heterogeneity, because there are variations in surgical procedure, patient characteristics, treatment duration and the definition of treatment outcome. Third, there are many studies which are only representative of orthopedic surgery populations and do not include other specialties of surgery. Comparative effectiveness research with a variety of surgical populations, elderly patients, patients with high bleeding risks, and real-world healthcare settings should be of particular interest in future investigations. For this reason, network meta-analysis methods

can provide additional insights into relative differences between different available anticoagulants when there are no direct comparisons.

6. Limitations and Future Research Directions

This systematic review/meta-analysis offers a thorough comparison of LMWH, rivaroxaban, apixaban and warfarin, but there are certain caveats to be borne in mind when extrapolating the results of this comparison. A major drawback is the clinical heterogeneity between studies available. There are significant variations in included investigations with respect to surgical procedures, patient characteristics, baseline thrombotic risk, duration of anticoagulant administration, and definitions of clinical outcomes. This variation can be significant enough to impact overall average estimates, and when assessing treatment effects in different clinical settings, introduce uncertainty. One drawback is that there are few head-to-head comparisons available for all four anticoagulant treatments. There has been a large number of randomized controlled trials that have compared individual DOACs with LMWH or warfarin-based therapy; however, there are relatively few studies directly comparing rivaroxaban, apixaban, LMWH and warfarin in essentially the same population of patients. Therefore, some comparisons are made based on indirect evidence and should therefore be interpreted with care.

This may be due to differences in study populations that can reduce generalizability. Much of the evidence available comes from populations of orthopedic surgery such as patients with total hip and knee arthroplasty, which may be a high-risk but distinct subset of postoperative patients. Anticoagulants may not be equally effective, or safe, in patients with complex medical comorbidities, patients with trauma surgery or patients who have cancer surgery or abdominal surgery. Also, the potential issues of medication adherence, healthcare providers availability, costs, and patient preference are also under-represented in randomized trials. DOACs offer benefits in terms of oral administration and a decrease in the need for monitoring, however these benefits could differ based on healthcare systems and patient factors. Further studies are needed focusing on very well-designed comparative effectiveness studies in broader populations of surgical patients directly comparing different anticoagulation approaches. Additional evidence for long-term effectiveness, safety, adherence, and cost effectiveness through large multicenter randomized trials and

prospective observational study would be valuable, taking into account the real-world clinical setting.

7. Conclusion

This systematic review and meta-analysis is predictive of the shifting guidelines of postoperative thromboprophylaxis and treatment of DVT. All LMWH, rivaroxaban, apixaban and warfarin are clinically significant anticoagulants with varying therapeutic profiles in terms of ease and frequency of administration, requirement for monitoring, bleeding risk, and ease of therapeutic use. LMWH is validated and proven to be a safe and used anticoagulant approach, especially in postoperative situations with widespread clinical experience and guidelines. However, DOACs have revolutionised anticoagulation with useful oral alternative agents having easily predictable pharmacological properties. Examining alternatives to these medications, rivaroxaban and apixaban show good proof of prevention of postoperative VTE and treatment of thromboembolic disease, and are appealing due to their convenience and the lack of monitoring. While there is no evidence of any single superior anticoagulant, the evidence does suggest that a patient-centered approach with the pros and cons of each therapy being considered is demonstrated. More well-designed comparative trials are needed to better understand long-term results and determine optimal anticoagulant choice and selection strategies in various surgical and thromboembolic patient populations.

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