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Systematic Review

A systematic review of anticoagulants evaluating efficacy and safety in thromboembolic disease

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ABSTRACT

Venous thromboembolism (VTE) is a major global source of morbidity and mortality. Oral anticoagulants have become a safer and more effective alternative to conventional anticoagulants, such as heparin and warfarin, which have been the cornerstone of treatment. They have shown comparable efficacy with fewer significant bleeding episodes. This study investigated the efficacy and safety of oral anticoagulants in comparison with other conventional anticoagulant therapies in patients with venous thromboembolism. A systematic review was conducted where data were obtained from PubMed, Scopus, Google Scholar, and Clinicaltrials.gov, covering the period from January 2020 to July 2025. Study selection was conducted in accordance with PRISMA guidelines and illustrated using a PRISMA flowchart. Eligible studies included randomized clinical trials, cohort studies, and observational studies that compared direct oral anticoagulants (DOACs) with conventional or other anticoagulant therapies. Data extraction was performed independently by two reviewers (EA), who identified relevant studies and extracted information on study characteristics, outcomes, and efficacy from the included articles. It was found that VTE is effectively managed with prolonged anticoagulation therapy. Research indicates that a minimum duration of three to six months of oral anticoagulant use significantly reduces the risk of recurrent VTE and is associated with fewer major bleeding events. Among the available options, a 20 mg dose of rivaroxaban has been shown to offer the highest efficacy. In contrast, monotherapy with agents such as vitamin K antagonists, aspirin, or warfarin is generally less effective, whereas combination therapy with oral anticoagulants provides improved outcomes. It is concluded that for patients with venous thromboembolism, direct oral anticoagulants are a safer and more efficient therapeutic option than vitamin K antagonists and traditional anticoagulation treatments.

Keywords: Venous thromboembolism, Anticoagulants, DOAC

INTRODUCTION

Venous thromboembolism (VTE) is a major cause of morbidity and mortality among hospitalized and community-dwelling patients, and its incidence rate is between 1.69 and 1.98 per 1000 individuals. In the general population, the mortality of VTE is estimated at 10 to 30 per cent. Thromboembolic disorders such as deep vein thrombosis (DVT), pulmonary embolism (PE), and atrial fibrillation-related stroke are continuing to be the causes of great morbidity and mortality across the globe.[1] The thromboembolic events have other chronic illnesses as risk factors, among them being chronic kidney disease (CKD). It is proportionately more compared to 13.4% in the overall population across the globe, and it is directly linked to the instances of VTE. The patients who undergo CKD level are ironically at high risk of bleeding. Many aspects of the pathophysiology in bringing forth conditions of a prothrombotic state accompanied by increased risks of bleeding present clinical decision-making concerning interventions of anticoagulation therapy, as a challenging scenario.[2]

Anticoagulant therapy can be essential to the prevention and management of such conditions.[3] Initially, the traditional treatment was glued to using conventional anticoagulants like unfractionated heparin (UFH) and vitamin K antagonists (VKAs) like Warfarin.[4] Direct oral anticoagulants (DOACs) are becoming a more preferred method of anticoagulation. However, their application in the treatment of acute venous thromboembolism (VTE) in severely obese patients (with a body weight over 120 kg or a BMI exceeding 40 kg/m²) remains unsafe. Consequently, the International Society on Thrombosis and Haemostasis has issued a cautious recommendation against their use in such patients.[5] A review was conducted on five observational studies involving 6,585 patients. The findings demonstrated that DOACs were not inferior to warfarin regarding major efficacy outcomes (VTE recurrence: OR 1.07, 95% CI 0.93–1.23) and secondary outcomes (petechial bleeding events) (OR 0.80, 95% CI 0.54–1.17). This indicates that the efficacy of DOACs is equivalent to that of warfarin in severely obese patients (body weight exceeding 120 kg or BMI over 40 kg/m²).[6]

A major source of chronic illness, VTE is a potentially preventable cause of death and a significant burden on healthcare budgets (comprising DVT and pulmonary embolism (PE). VTE affects all patients undergoing joint replacement surgery, as they have lengthy operations and limited mobility immediately afterwards. To reduce this risk, nearly all patients receive anticoagulant treatment for up to 35 days following the surgery.[7] The incidence of VTE after 90 days of THR and TKR varies, with the highest rates being 5 per cent for DVT and 2 per cent for PE in those who had not previously been anticoagulated. The anticoagulants used to avoid VTE are easier (orally, e.g. aspirin), injectable (low-molecular-weight heparin (LMWH)), and newer and easier to use (e.g. dabigatran etexilate, rivaroxaban). Aspirin is cheap to administer, simple to transport, and has an outstandingly good safety record. In the United States, as well as in the United Kingdom, aspirin is nowadays administered off-label in the prevention of VTE.[8]

Pediatric patients who experience VTE are likely to experience morbidity and even mortality. UFH, low-molecular-weight heparin (LMWH), and vitamin K antagonist were the main modalities for thrombotic events in children previously. However, since the approval of the first non-vitamin K warfarin (NOAC) for use in adults, this category of medicines has become popular in terms of various applications.[9] The implementation of these is attributed to the convenience of use, good pharmacokinetics and pharmacodynamics features, reduced food interference, and reduced therapeutic drug monitoring requirement. Among the numerous issues of the child population is treating and preventing VTE with the help of conventional anticoagulants. In the current systematic review, the authors' overview of the existing activity in the study of pediatric trials of NOAC.[10]

Best prevention practices against VTE currently comprise oral anticoagulants (e.g. factor Xa inhibitors, direct thrombin inhibitors, and warfarin) and subcutaneous anticoagulants (e.g. low molecular weight heparin (LMWH) and fondaparinux). In patients with early-stage CKD, however, recent evidence suggests that there may be a more positive benefit-risk profile associated with direct oral anticoagulants (DOACs) over vitamin K antagonists (VKAs). A Bayesian network meta-analysis has indicated that with the use of dabigatran, edoxaban, apixaban, and rivaroxaban in patients, there is a reduced risk of intracranial haemorrhage compared to when patients are under warfarin. Although the comparative trials of DOACs on a large scale are not yet available, a retrospective study has mentioned that apixaban is linked with a greater reduction in VTE recurrence and bleeding than rivaroxaban.[11]

Even though the suggested advantages and clinical conveniences of the DOACs over the established conventional anticoagulants have been documented, they are relatively novel techniques with nothing in use on the CKD population. Moreover, the use of other types of anticoagulants, namely, heparin or warfarin, is still quite common in such a population as opposed to DOACs due to interindividual differences in the renal clearance of DOACs as well as the absence of available randomised controlled trials.[12]

DOACs are reported to be capable of reducing the risks of ischemic stroke, major haemorrhage, and intracranial haemorrhage (ICH), not to mention the risk of gastrointestinal (GI) bleeding in patients with atrial fibrillation (AF) having some form of liver malfunction, without any substantial influence on GI bleeding as compared to warfarin.[13]

This study is planned to study the efficacy and safety of oral anticoagulants in comparison with other conventional anticoagulant therapies in venous thromboembolism patients.

METHODS

This analysis was developed methodically and presents the specific objective, inclusion criteria of studies, procedure for assessing the quality of studies, findings, and statistical methods. This review was registered on PROSPERO (ID: CRD420251107705).

Inclusion criteria

This systematic review encompassed randomized controlled trials, cohort studies, observational studies, and retrospective studies assessing the efficacy and/or safety of DOACs in comparison to conventional anticoagulation therapies for patients diagnosed with VTE. Eligible studies included adult or pediatric populations with deep vein thrombosis or pulmonary embolism and reported at least one clinically significant outcome, such as VTE recurrence, bleeding episodes, death, hospitalization, or composite thrombotic endpoints. Only full-text publications published in English from January 2020 to July 2025 were included.

Exclusion criteria

Studies were excluded if they were reviews, meta-analyses, case reports, conference abstracts, expert opinions, animal experiments, or if they lacked suitable comparators or quantifiable clinical outcomes. Other reasons for exclusion were populations who were not VTE, interventions that were not anticoagulants, publications that were not in English, studies that were published before 2020, or studies that did not have enough data for meaningful synthesis.

Data sources and searches

We identified all published studies that compared the risk of venous thromboembolic events in patients randomized to DOACs (Enoxaparin, Apixaban, Warfarin, and Heparin) or any conventional anticoagulant therapy using the MEDLINE/PubMED (January 2021 to July 2025) and Google Scholar (January 2021 to July 2025) electronic databases. The search methods were planned with a language limitation to English and with both the medical subject headings and keywords of the online-only data. Researchers went further to use the references of every article gathered manually. The researcher also searched the www.clinicaltrials.gov website to identify unpublished trials.

Study selection

Two reviewers performed the process of selecting the studies separately. The differences of opinion that occurred were described and solved by discussion, and where a third person was needed to help in a decision, one would consult. Studies that were researched and were potentially qualified to be included in this systematic review had one particular requirement, namely, they had to be either phase III randomized controlled trials (RCTs) or phase II RCTs reporting at least some of the dosages that were used in the phase III studies. Moreover, the researchers had to compare novel oral anticoagulants (NOACs) in patients with bleeding and thromboembolic events in the two groups, necessary to be characterized in objectively-determined ways. In the case of the synthesis of the results of published trials, the researcher used the data from the most complete publication that we were able to find and mentioned other publications to elucidate findings.

Data extraction and quality assessment

We organised, gathered data and provided it as done by providing innovative service models and assessment (PRISMA). The data on the study (year of publication, design), study population (number of patients) and on the treatment (therapeutic indication) were extracted separately by two reviewers. Moreover, the quality of the studies was determined by the two reviewers with the help of a well-known scale for assessing based on Cochrane's particular criteria (ROB2) (Figure 1).

RESULTS

A total of 1,483 study titles were found in the database search. Only 710 titles were generated as RCTs, cohort studies, observational studies and retrospective studies. After eliminating the papers that did not meet the initial search criteria, researchers selected 520 abstracts for screening; only 9 were eligible for final review. The PRISMA flowchart illustrates the study selection procedure, as shown in Figure 2.

This study comprised nine studies that satisfied the inclusion criteria. Each study's patient population is very distinct. Shorter stays were recorded in every study that employed the DOAC treatment. Table 1 summarizes the characteristics of the study.

Dosage and duration of treatment

VTE requires anticoagulation for a minimum of three to six months.

A study showed that 6 months of DOAC resulted in no VTE and fewer bleeding events. Compared to those who did not receive prolonged DOAC therapy, those who did had lower composite major bleeding and recurrent VTE risks.[18]

The dosage of treatment for the recurrence of thromboembolism and bleeding events was also examined. In one of the studies, 20 mg of rivaroxaban was found to be more effective.[15]

Efficacy of oral anticoagulants

In the acute phase of venous thromboembolism (VTE), direct oral anticoagulants (DOACs) are advised as the first-choice anticoagulation treatment.[19] Compared to VKAs, Apixaban and Rivaroxaban had a significantly lower hazard ratio for hospitalisation, bleeding, and all-cause death.[17] When compared to aspirin alone, rivaroxaban plus aspirin was associated with a lower incidence of VTE. Compared to patients receiving direct oral anticoagulants, patients on conventional anticoagulant therapy experienced bleeding events during anticoagulation more frequently (4.2%). Compared to patients receiving warfarin, patients without the medication had a greater cumulative rate of recurring symptomatic VTE. Warfarin treatment works well without raising the risk of bleeding problems.[14]

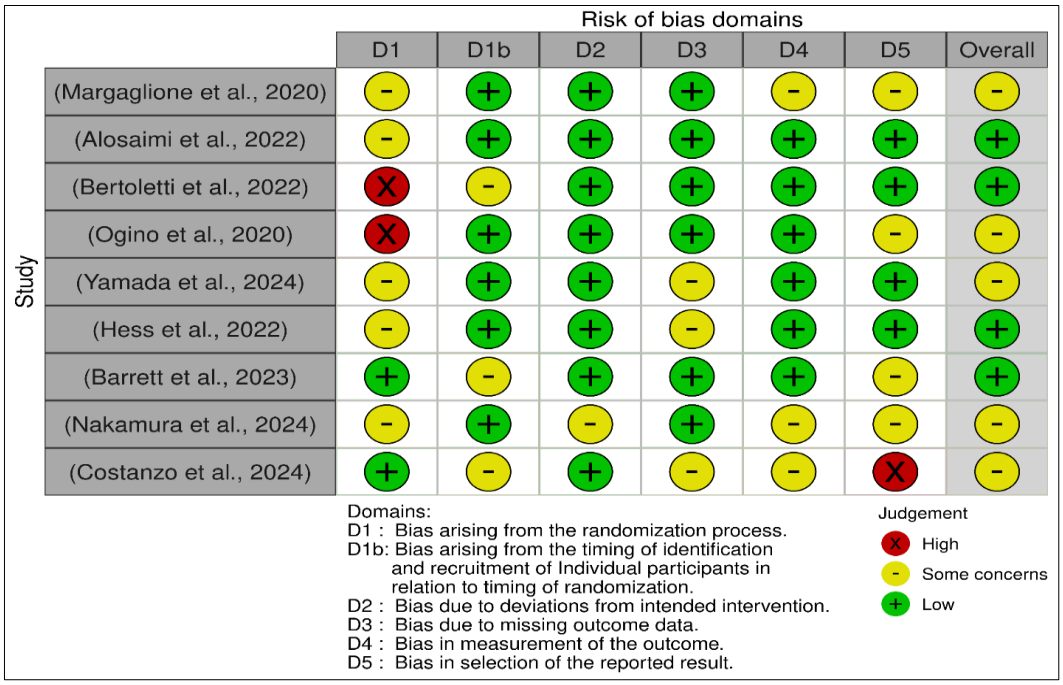

Figure 1: Risk of bias domain versus study.

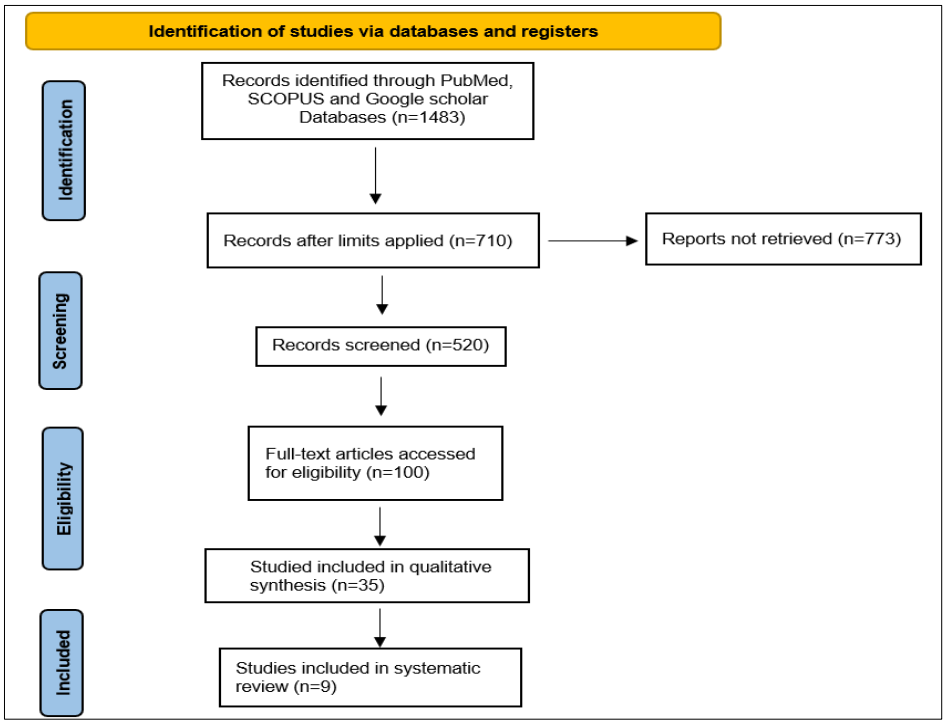

Figure 2: PRISMA flowchart.

Table 1: Characteristics of the study included in the current review.

Reference	Study type	Condition	Intervention	N	Primary outcome	Significant
15	RCT	Venous thromboembolism	Oral anticoagulants	4866	Oral anticoagulants are more effective than conventional anticoagulant therapy	Yes
16	Retrospective observational study	Venous thromboembolism	Rivaroxaban	2316	Rivaroxaban 20 mg reduced safety events like thrombosis, stroke, and bleeding	Yes
17	Observational study	Venous thromboembolism	Direct oral anticoagulants	58,137	DOACs are safer and more effective than vitamin K antagonists	Yes
18	Retrospective study	Cancer-associated venous thromboembolism	Direct oral anticoagulants	1,096	Prolonged DOAC therapy reduces bleeding and VTE recurrence risks	Yes
19	Prospective long-term observational study	Venous thromboembolism	DOACs	1,017	DOAC result in fewer bleeding events	Yes
20	Multicenter cohort study	Venous thromboembolism	ASA (acetylsalicylic acid) along with rivaroxaban	6564	Low-dose rivaroxaban reduces VTE risk significantly	Yes
21	RCT	Venous thromboembolism	ASA and rosuvastatin	112	ASA and rosuvastatin with VTE prophylaxis reduced VTEs safely	Yes
14	Prospective study	Venous thromboembolism	Warfarin	352	Warfarin therapy is effective and safe	Yes
22	Retrospective study	Venous thromboembolism	Direct oral anticoagulants	185	Long-term DOAC therapy is similar in efficacy and safety	Yes

Safety of oral anticoagulants

Significant bleeding during treatment was the main safety outcome measure. A study included in the review showed that using lower dosages of Apixaban (2.5 mg BID) and Rivaroxaban (10 mg OD) for treatment is both safe and effective.[22] In one study, rivaroxaban, edoxaban, and apixaban were administered to 374, 367, and 252 patients, respectively. Results showed that major bleeding, the primary safety endpoint, occurred in 22 patients (2.2%), which translates to an incidence rate of 2.6% per patient-year (95% CI, 1.5–3.7%). Six patients (0.6%) experienced cerebral bleeding, nine (0.9%) experienced gastrointestinal bleeding, seven (0.7%) experienced various bleeding events (such as uterine haemorrhage, haematuria, and bleeding from the procedure site), and non-fatal bleeding.

DISCUSSION

VTE continues to be a major cause of morbidity and death following an accident. Rosuvastatin, an inhibitor of beta-hydroxy beta-methylglutaryl-CoA (HMG-CoA) reductase, was shown in a previous experiment to considerably lower pathologic clotting events in healthy persons. Nevertheless, more recent decades have seen the appearance and growing use of newer types of oral anticoagulants, such as enoxaparin, apixaban, warfarin, and heparin (in low molecular weight variety), that have significantly changed treatment methods.[23] The systematic review of the comparative efficacy and safety of said agents revealed that oral anticoagulants are clinically better than the routine agents in the setting of thromboembolic disease.[24]

Direct oral anticoagulants had beneficial results regarding efficacy and safety in the research reviewed, with many studies indicating a decreased recurrence of VTE and a reduction in significant bleeding incidents relative to traditional anticoagulants. These results are in line with recent large-scale comparative studies that have demonstrated that rivaroxaban and apixaban lower the risk of having thrombotic events again without increasing the risk of clinically severe bleeding when compared to vitamin K antagonists and LMWH.[17,19] A network meta-analysis performed in 2024 similarly determined that apixaban exhibited the most advantageous composite

profile for efficacy and bleeding risk, whereas rivaroxaban showed robust efficacy with marginally elevated gastrointestinal bleeding rates, consistent with the trends identified in this review.[25] The overall uniformity of results indicates that DOACs may provide a more balanced therapeutic profile in both acute and prolonged VTE treatment phases, especially when long-term continuation is necessary.

Among the most important topics found in the review is the steady and improved prevention of thromboembolism when using oral anticoagulants.[26] The randomized controlled trial (RCT) and meta-analysis studies have continuously proven that compared to the traditional treatment, the combination of Apixaban and Enoxaparin has a remarkably lower frequency of the second occurrence of DVT and PE.[27] An example is the AMPLIFY trial that noted that, in addition to the fact that Apixaban achieved a reduced thromboembolic recurrence, it did so with a reduced major bleeding occurrence compared with conventional heparin/warfarin combinations.[28]

Low molecular weight heparin (LMWH), such as enoxaparin, has a multiplicatively more predictable pharmacokinetic profile and can be administered in fixed doses without regular monitoring.[29] In several studies (namely Matisse-DVT and Matisse-PE), Enoxaparin was shown to be at least as efficacious as the standard UFH in the initial and extended treatment of venous thromboembolism (VTE), with fewer adverse effects and reduced length of hospitalization.[30] Although technically warfarin can be counted as a traditional agent, it has also proven to be better than placebo and aspirin in preventing the occurrence of stroke in patients with atrial fibrillation.[31] Specifically, the BAFTA trial highlighted the value of Warfarin in preventing strokes by almost 60 per cent among older persons with atrial fibrillation, and this has further enforced its application in thromboembolic prevention.[32]

LHMWH, in fact, can outperform the use of UFH too, and now has fewer incidences of heparin-induced thrombocytopenia (HIT) and more predictable anticoagulation effects.[33] The change of intravenous UFH to subcutaneous LMWH, like Heparin and Enoxaparin, is one step forward in terms of patient comfort and convenience as well as the efficient method of treatment.[34]

Safest anticoagulant treatment and, in particular, the risk of major bleeding are primary concern that influences clinical decision-making.[35] Analysis of the studies reviewed shows that the safety profile of the use of oral anticoagulants is most favourable when compared to conventional therapies.[36] Such drugs as apixaban, for example, have been linked with the reduced rate of intracranial haemorrhage and gastrointestinal bleeding both in cases of acute treatment and secondary prevention.[37] Apixaban is effective as well as safer, and in a 31 per cent reduction of the major bleeding rates in patients with non-valvular atrial fibrillation in the ARISTOTLE trial, where the study compared the results of Apixaban with Warfarin.[38]

Enoxaparin has also been linked to fewer complications in terms of bleeding as compared to UFH.[39] The fact that it is roughly predictable by a dose-response relationship reduces the chances of supratherapeutic anticoagulation, which frequently occurs when using UFH, and has wide-ranging hemorrhagic side effects.[40] Although Warfarin is indeed more dangerous as it causes bleeding when compared to such new agents as Apixaban and Rivaroxaban, particularly in the first stages of treatment, the bleeding risks associated with Warfarin can be neutralised via the meticulous monitoring of the international normalised ratio (INR).[41] However, there is a convenient and safer alternative that involves newer compounds that do not demand regular tests, Apixaban and Enoxaparin, among others, and treat numerous groups of patients equally well.[42]

Along with effectiveness, the safety profile of DOACs was a key part of the research that was looked at. Our findings that extended low-dose DOAC therapy diminishes the risk of significant bleeding are corroborated by numerous recent observational cohorts indicating a lower incidence of cerebral haemorrhage and gastrointestinal bleeding in comparison to warfarin.[43] Furthermore, registry data from post-marketing surveillance studies indicate enhanced patient adherence to DOACs, attributed to reduced monitoring requirements and the absence of food restrictions—elements linked to increased treatment continuity and diminished variability in anticoagulation levels.[44,45] These findings significantly bolster the assertion that DOACs not only equate to but may exceed traditional anticoagulants in terms of safety and long-term patient management. This indicates a persistent transition in existing clinical practice guidelines towards more DOAC application in VTE care.

Another important benefit of the new oral anticoagulants is the ease of use, which is much easier as a result of which there is less non-adherence to the medication and thus, better patient outcomes.[46] Apixaban and Enoxaparin can be given at fixed doses without frequent monitoring in the laboratory and dose alterations, as compared to Warfarin, which requires routine checking of the INR and dose alteration.[47] Enoxaparin as medicine in surgery and in the hospital environment is particularly indication-friendly because of its short half-life and the subcutaneous entry.[48] Yet, oral medications, i.e. Apixaban, possess the added advantage of being outpatient in nature, which helps in early discharge of the patients and in the comfort of their homes, which is more beneficial in terms of cost, allocation of resources and the comfort of the patient.[47]

Moreover, there are dietary restrictions and drug-drug interactions characteristic of Warfarin, which are almost absent with newer ones.[49] Patients who use Warfarin with vitamin K dietary precision are liable, and its metabolism

depends on several CYP450 enzymes, making it respond to various drug interactions.[50] Instead, Apixaban shows low food interactions and more predictable metabolism, which increases compliance and therapeutic stability even further.[51]

The review also recorded the performance of newer oral anticoagulants in special patient groups, such as cancer-risk thrombosis, orthopaedic surgical patients, and patients with renal impairment.[52] Both enoxaparin and Apixaban have been examined in some detail in cancer-related thrombosis, with indications that they are associated with lower recurrence of VTE and less bleeding than standard treatments. Apixaban and Enoxaparin have proved effective in thromboprophylaxis in orthopaedic patients who undergo hip or knee surgery replacements, and they are frequently superior to Warfarin in terms of bleeding risk and management. Such agents have also proved to be of utility in the medically-ill hospitalised patient population at risk of thromboembolism, which have prophylactic effects without increases in the risk of haemorrhage as observed with UFH.

In patients with renal impairment, where management of anticoagulation is especially difficult, the new oral anticoagulants (at altered dosing) have shown acceptable safety. Nonetheless, this is not without caution, especially when it comes to the LMWHs, which are renally cleared. Warfarin can be helpful in severe renal dysfunction because it is hepatally metabolized; however, its fluctuation and the need to monitor it make it prohibitively used in unstable patients.

Although newer oral anticoagulants cost more per dose than Warfarin or UFH, the cost-effectiveness of newer oral anticoagulants, such as Apixaban and Enoxaparin, emerges when the total cost of care is considered. The lower frequency of INR monitoring, decreased hospitalization due to bleeding, inpatient stay, and the decreased frequency of recurrent thromboembolism has all led to the lower cost of long-term healthcare. In addition, outpatient regimens are associated with maintenance of patient productivity and quality of life, and in chronic anticoagulation, this is of special importance.

The reviewed anticoagulants do have a number of merits, but they do not lack limitations. Newer anticoagulants do not have reversal agents, and reversal agents are still under development. As an example, though the reversal of inhibitors of factor Xa, such as Apixaban, is supported by the administration of Andexanet alfa, it is not universally found, and its price is a restriction in most situations. In comparison to Warfarin, vitamin K and Plasma transfusions can reverse Warfarin, thus making it easier to handle in case of emergency bleeding.

Furthermore, the long-term outcomes and compliance reported with newer oral anticoagulants are yet to amass real-world data. Post-marketing surveillance and large-scale registry studies remain a vital means of proving the effectiveness of clinical trials in a wider population of patients that reflects those served by a given medical facility.

According to the systematic review, clinicians are advised to base the decision of selecting anticoagulants through a patient-centred approach. Even though Apixaban and Enoxaparin are found to be more efficient and safer in most thromboembolic conditions, Warfarin can still be applied in certain situations, e.g., mechanical heart valve or severe renal insufficiency. The most important thing entails the personalisation of the anticoagulation approaches so as to focus on the personal aspects of the patient considerations, such as the presence of comorbidities, the possibility of bleeding and kidney complications, and the risk of drug interaction.

In the majority of thromboembolic diseases, it is now becoming a norm that the American College of Chest Physicians (ACCP), the European Society of Cardiology (ESC), and the National Institute for Health and Care Excellence (NICE) publication of guidelines caution the usage of the latest oral agents like Apixaban and LMWHs as the primary treatment option. Such suggestions agree with the facts provided in this review, revealing the trend of moving towards more efficient, safer and patient-friendly treatments.

This systematic review reveals the fact that oral anticoagulant agents, and most especially Apixaban, Enoxaparin, Warfarin, and Heparin (LMWH), are better and safer relative to conventional anticoagulants in treating thromboembolic diseases. These are predictable pharmacology, lower risk of bleeding, increased convenience in use by patients and clinical flexibility, which represent an important advance in anticoagulant treatment.

There is much untapped potential in these transformative therapies, and future research will endeavour to enlarge the real-world evidence, enhance reversal protocols and address the challenges in special populations to make these therapies accessible in their full potential.

CONCLUSION

Direct oral anticoagulants are a safer and more effective treatment than conventional anticoagulation therapies and vitamin K antagonists for venous thromboembolism patients.

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