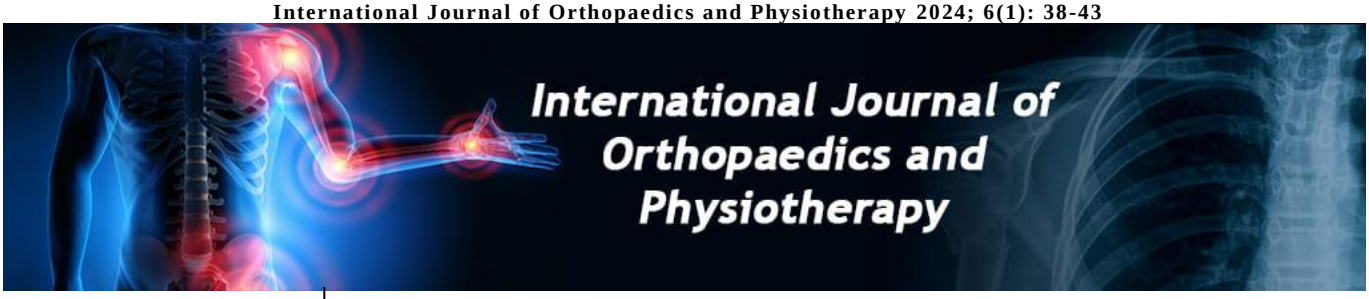

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Prophylactic anticoagulants in arthroplasty: Review of article

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Abstract
Background: Venous Thromboembolism (VTE) is a significant condition that is known to be present after total hip or knee replacement, and anticoagulants therapy as a prophylaxis is currently the treatment option. The study was carried to assess the efficacy of various anticoagulants in the reduction-of-individual VTE risk after these operations.
Objectives: To carry out detailed network meta-analysis of effectiveness of all anticoagulants for the prevention of VTE after total hip or knee arthroplasty.
Methods: One systematic review, network meta-analysis of the mentioned studies was performed, in which anticoagulant medications was given after total hip or knee arthroplasty. The main outcome measures were Deep vein thrombosis (DVT) and pulmonary embolism (PE).
Results: The study evaluation process comprised 18 studies looking at the effects of eight anticoagulants. Regarding DVT prevention, apixaban, edoxaban, fondaparinux, and rivaroxaban proved to be more effective than other agents in this class. There were no signifcant differences in respect of PE prevention for the anticoagulants.
Conclusion: This systematic evaluation revealed a better efficiency of apixaban, edoxaban, fondaparinux and rivaroxaban in preventing DVT following THA/TKA than the other anticoagulants. The use of NOACs would increase the effectiveness of patient management and reduce the morbidity of DVT.

Keywords: Venous thromboembolism, arthroplasty, patient management, pulmonary embolism

Introduction
Venous thromboembolism (VTE) which comprises of deep vein thrombosis (DVT) and pulmonary embolism (PE) are huge challenges facing the healthcare sector nowadays. [1] According to the WHO report, each year VTE affects approximately 10 million people globally [2]. This implies that it ends to be the third most common acute cardiovascular disease syndrome after MI and stroke, respectively [3]. VTE also brings dire consequences as it increases the morbidity and mortality rates after patient's admission to the hospital [4] and it also has economic implications on healthcare systems worldwide [5]. THA and TKA are two hip and knee replacement surgeries that are said to be more than 95% successful treatments with the ability to alleviate chronic joint pain, improve mobility, and consequently, enhance patients' quality of life. On the other hand, the surgical procedures are not free from risks and VTE is still one of the major problems that need to be overcome with caution. The use of anticoagulants stands as the mainstay of pharmacological postoperative measures against VTE (venous thromboembolism). The spectrum of anticoagulant drugs is huge, and each of them works in its own way and presents its own set of side effects and contraindications. While moving through this tangled maze is not easy, since there is no agreement on the comparability of these drugs in preventing VTE after either THA or TKA, there are claims that the risk of VTE is not significantly reduced by any of them. This study intends to carry out a systemic network meta-analysis, as a way of providing more information about different anticoagulants (that aim at preventing VTE post-surgery). Therefore, our investigations have important implications given that they can provide healthcare practitioners with scientific data to help them in designing VTE prevention strategies that suit patients, hence improving patient outcomes and reducing the intense workload of VTE management.

Search Strategy

A comprehensive literature search was conducted by two independent reviewers, scouring various databases, including PubMed, Embase, The Cochrane Library, Web of Science, CBM, CNKI, Wan Fang Data, and VIP. The search encompassed studies published between January 1, 2000, and January 27, 2022. To ensure a thorough and exhaustive exploration, the references listed in the included studies were also meticulously traced to supplement relevant data.

Eligibility Criteria

The criteria for inclusion and exclusion criteria were designed to be broad and flexible, so that studies that used anticoagulant after total hip replacement (THA) or knee replacement procedure (TKA), irrespective of the age, race, nationality of the patients and subjects will not be excluded. We did not set a priori the types of the studies that would be included except retrospective and prospective studies to be in the scope of this review. Their outcomes, including the number of responders and sample size would have been required to be available and presented.

The exclusion criteria were specifically chosen to eliminate studies that deviated from the main objectives of the review. The following kinds of documents were denied ; the duplicate articles, studies with inconsistent research content, review studies, conference abstracts, animal studies, case reports, protocol studies which would not be included. Also, the papers which were non-English were excluded.

Literature selection and Data harvesting

A precise and comprehensive approach was followed during the literature screening/data extraction. Two reviewers were engaged to scan the studies that were identified, first by scanning the titles and abstracts and thereafter by reading fully the plausible articles so as to determine which ones were appropriate for the final analysis.

The procedure of data extraction was also demanding, as reviewed authors performed it independently, and all data of interest were extracted from studies and cross-checked. Among others, information regarding the author, publishing year, country, the type of anticoagulant used, the age of study participants (male and female), and kind of surgical procedure (performed) was extracted from the obtained data. To further underscore this, the study results compared the sample size and the number of respondents.

The third party was with us when we had conflicts during the literature screening or data extraction; they helped us to bring the disputes to an objective and impartial resolution.

Statistical analysis

In the course of a complete study, we critically analyze the transitivity among the involved studies by comparing their basic elements which have been taken in consideration and examined meticulously thus having a careful foundation that is compatible and can be used in our studies. The heterogeneity among the studies was comprehensively evaluated by means of I^2 statistic, a measure that quantifies the extent of variability beyond what would be expected due to chance.

When the I^2 value fell below 50%, which means less heterogeneity among studies, a fixed-effect model was utilized to combine the data so we could produce an estimation with good accuracy and precision. Nonetheless, if the I^2 value was over 50%, which was a sign of significant heterogeneity, it was explored further through meta-regression that is designed to address the potential sources of this variability. We were flexible to recognize the factors that may have attributed to this heterogeneity and, therefore, we could perform subgroup analyses to provide better precision on our findings.

When we were not able to point out the source of heterogeneity in spite of our all feasible efforts, we adopted a random-effects model for pooling to make certain our conclusions were not influenced by the random influences of heterogeneity.

Being aware of the significance in our analysis of the degree of consistency in analysis, we discussed both global and local inconsistencies paying attention to details. Global Wald test was chosen for the investigation of global inconsistency; while the node-splitting test was included for the examination of local inconsistency. In case the findings of direct and indirect contrast failed to yield statistically significant differences (p> 0.05), meaning good consistency, we applied an inconsistency model for pooling. In this case, on the other hand, when inconsistencies were detected, we used inconsistency model to guarantee that the results of our study will not be subject to any flaws.

To assess the efficacy of the anticoagulants under study, we adopted RR (relative risk) and 95% confidence intervals (CI) as our key measures. Furthermore, we resorted to P score parameter, to rank and compare the anticoagulants that have been discussed, and anticoagulant that gets higher score outcome has better ranking.

To ensure the overall homogeneity of the results, we ran thorough credibility checks which are of vital importance for correctness and consistency of our test. Using a procedure of step-wise exclusion of the studies included in the original analysis and repeating the whole meta-analysis run we calculated their effects and compared them with the original. If after the implementation minimal changes happened it meant that robustness of literature included was high and our study was reliable.

Overall, we used the combination of statistical methods, including the Egger, Begg-Mazumdar and Thompson-Sharp tests, in order to evaluate the possibility that publication bias may be present in the sample. The fact that the outcomes of these tests all showed P values above 0.05 also gave us the confidence to declare that there was no sign of publication bias, thus strengthening the validity of our results. Nevertheless, if publication bias was discovered we would bear that in mind and draw conclusions with due caution.

Results

To start with, 12 anticoagulants were drawn up from studies reviewed and 70 researches were found through surveys. Eventually, 18 articles assessing the efficiency of eight anticoagulants, undergone a multistage screening, were put into the review. The 8 potent anticoagulants here mentioned are apixaban, aspirin, betrixaban, edoxaban, fondaparinux, low molecular weight heparin (LMWH), rivaroxaban, and unfractionated heparin (UFH). The detailed data about involved studies is shown in the Table 1. Such rigorous selective and focused scrutiny resulted into a thorough examination of the efficiency of these potent anti-clotting products.

Table 1: Details of the analyzed studies

Country	Surgery type	Recipients (M/F)	Age	Anticoagulant	Study
Turkey	THA	51 (13/38)	53.2 ± 9.4	LMWH	*et al* 2005 [6]
		52 (19/33)	52.4 ± 11.2	UFH	
Canada	THA	906 (384/402)	69 (26-92)	Fondaparinux	Turpie, *et al* 2002[7]
		921 (375/426)	69 (19-91)	LMWH	
Canada	TKA	102 (36/66)	69 (49-85)	Rivaroxaban	Turpie *et al*, 2005 [8]
		105 (48/57)	67 (48-83)	LMWH	
Canada	TKA	1528 (520/1008)	65.3 ± 9.8	Rivaroxaban	Turpie, *et al* 2009 [9]
		1510 (542/968)	64.8 ± 9.9	LMWH	
Canada	TKA	86 (33/53)	66 (48-75)	Betrixaban	Turpie *et al*, 2009 [10]
		45 (22/23)	64 (44-75)	LMWH	
China	TKA	52 (11/41)	65.15 ± 8.95	Rivaroxaban	Shi *et al*, 2014 [11]
		27 (8/19)	66.85 ± 6.92	LMWH	
China	TKA	62 (36/26)	68.4 ± 0.7 (55-76)	Rivaroxaban	Wang *et al* 2014[12]
		62 (37/25)	67.7 ± 0.5 (58-77)	LMWH	
Japan	THA	86 (15/71)	65.0 ± 11.0	Fondaparinux	Yokote *et al* 2011[13]
		86 (18/68)	66.0 ± 12.0	LMWH	
China	THA	72 (40/32)	57.67 ± 10.25	Rivaroxaban	Yang *et al* 2013 [14]
		73 (38/35)	59.53 ± 10.67	LMWH	
China	THA	42 (23/19)	58.39 ± 9.66 (49-69)	LMWH	Zhang *et al* 2017 [15]
		47 (29/18)	57.69 ± 9.38 (47-68)	Rivaroxaban	
China	TKA	99 (30/69)	69.5 ± 3.9	Rivaroxaban	Wang *et al* 2020 [16]
		100 (35/65)	70.76 ± 4.7	LMWH	
China	THA	67 (28/39)	72.3	Rivaroxaban	Wu *et al* 2013 [17]
		68 (30/38)	77.7	LMWH	
China	TKA	104 (33/71)	63.9 (52-82)	Rivaroxaban	Zou *et al* 2014 [18]
		112 (20/92)	65.7 (54-80)	LMWH	
		111 (28/83)	62.7 (47-79)	Aspirin	
China	TKA	47 (20/27)	57.48 ± 10.12	LMWH	Zhang *et al*, 2020 [19]
		45 (22/23)	59.85 ± 8.23	Rivaroxaban	
		91 (45/46)	63.78 ± 7.39	LMWH	
Canada	TKA	78 (22/56)	67.2 ± 8.8	LMWH	Weitz *et al*, 2020 [20]
		87 (20/67)	64.7 ± 8.6	Apixaban	
Egypt	THA	82 (37/45)	42.97 ± 10.8	Rivaroxaban	Rahman *et al*, 2020 [21]
		82 (45/37)	40.12 ± 14.9	LMWH	
USA	THA	175 (66/109)	57.8 ± 12.55	LMWH	Raskob *et al*, 2010 [22]
		185 (67/118)	58.2 ± 11.52	Edoxaban	
China	THA	34 (14/20)	54.7 (40.9-62.4)	Aspirin	Ren *et al*, 2021 [23]
		36 (11/25)	50.0 (36.8-57.0)	Rivaroxaban	

Meta-Analysis results

Close inspection of the input studies revealed that they were highly related to each other, which indicated that the hypothesis of transitivity was probably valid in the given data set. The heterogeneity assessment demonstrated a moderate level for DVT outcome (I^2 = 44.8%) and no detectable heterogeneity for PE outcome (I^2 = 0.001%).

Notably, no global inconsistency was detected, neither for the DVT outcome (global Wald test: P=0.685) nor for the PE outcome (global Wald test: P=0.980). Furthermore, the analysis uncovered no local inconsistency for the DVT outcome (Table 2) or the PE outcome (Table 3). Guided by these findings, the consistency model and fixed model were employed for pooling the data. There was no significant difference in comparisons of the efficacy of the eight anticoagulants for the prevention of PE

In terms of prevention of DVT,

A.

Efficacy of apixaban was better than that of LMWH (RR = 0.38, 95% CI: [0.26-0.62]), aspirin (RR = 0.37, 95% CI: [0.21-0.63]), betrixaban (RR = 0.32, 95% CI: [0.09-0.97]).

B.

Efficacy of edoxaban was better than that of LMWH (RR = 0.45, 95% CI: [0.29-0.67]), aspirin (RR = 0.42, 95% CI: [0.24-0.74]), UFH (RR = 0.39, 95% CI: [0.25-0.69]), betrixaban (RR = 0.35, 95% CI: [0.09-0.89]).

C.

Efficacy of fondaparinux was better than that of LMWH (RR = 0.57, 95% CI: [0.38-0.76]), no.9 aspirin (RR = 0.57, 95% CI: [0.33-0.73]), UFH (RR = 0.51, 95% CI: [0.43-0.63]), and warfarin (RR = 0.31, 95% CI: [0.24-0.40]).

D.

Efficacy of rivaroxaban was better than that of LMWH (RR = 0.59, 95% CI: [0.58-0.68]), aspirin (RR = 0.56, 95% CI: [0.39-0.77]).

Dissecting the fine details of anticoagulant efficacy, we performed an in-depth investigation on their role in preventing deep vein thrombosis (DVT) and pulmonary embolism (PE). The P score, a metric that illuminates the relative potency of each agent, revealed a fascinating hierarchy for DVT prevention: apixaban took the first place, followed by edoxaban, fondaparinux, rivaroxaban, low molecular weight heparin (LMWH), aspirin, UFH, betrixaban and finally, warfarin (Table 4). In the realm of PE prevention, the P score unveiled a subtly different order: although apixaban was the most prominent drug, aspirin came in a close second, rivaroxaban was the next,

fondaparinux also stood out, and the remaining were edoxaban, LMWH, betrixaban and UFH respectively (Table 5).

Table 2: Node splitting test results for DVT.

Comparison	P-Value
LMWH vs apixaban	.680
Aspirin vs LMWH	.447
Aspirin vs rivaroxaban	.878
Fondaparinux vs LMWH	.472
LMWH vs rivaroxaban	.178
LMWH vs UFH	.612

Table 3: Node splitting test results for PE.

Comparison	P-Value
LMWH vs apixaban	.581
Aspirin vs LMWH	.567
Aspirin vs rivaroxaban	.457
Fondaparinux vs LMWH	.717
Fondaparinux vs UFH	.752
LMWH vs rivaroxaban	.428
LMWH vs UFH	.911

Table 4: The *P* score for prevention of DVT.

Anticoagulants	P-Score	Rank
Apixaban	.955	1
Edoxaban	.922	2
Fondaparinux	.767	3
Rivaroxaban	.734	4
LMWH	.374	5
Aspirin	.316	6
UFH	.253	7
Betrixaban	.219	10

Table 5: The *P*-Score for prevention of PE.

Anticoagulants	P-Score	Rank
Apixaban	.712	1
Aspirin	.688	2
Rivaroxaban	.603	3
Fondaparinux	.587	4
Edoxaban	.478	5
LMWH	.405	6
Betrixaban	.317	7
UFH	.244	8

Discussion

Venous thromboembolism (VTE) is a prevalent and escalating condition, inextricably linked to severe capillary disease and substantial treatmentburdens [24]. The primary catalyst for VTE's occurrence lies in the hypercoagulable state that ensues following joint replacement surgery, where the body's coagulation mechanisms are activated, procoagulant substances such as fibrinogen and thromboxan surge, and the inflammatory edema of the surgical site leads to blood vessel compression, thus sluggish local blood flow [25]. Consequently, to effectively prevent VTE after total hip arthroplasty (THA) or total knee arthroplasty (TKA), reliance on compression stockings, pneumatic compressions, bed rest, and other general measures alone is insufficient, systematic anticoagulant therapy must be incorporated.

Our survey study on the efficacy of 8 anticoagulants used in THA or TKA procedures specifically was a rigorous review, using both direct comparisons and indirect ones to evaluate their quality. Among the antithrombotic agents that are used in the prevention of deep vein thrombosis (DVT), the league table together with the P score results revealed apixaban, rivaroxaban, edoxaban, fondaparinux, and darexaban as the anticoagulant products of the highest efficacy for these surgical methods. Nevertheless, the low frequency of pulmonary embolism (PE) makes it difficult to detect any significant differences in effectiveness among anticoagulants via the league table and P Score, since it approaches zero. Among the important representatives of this category, we can list apixaban, edoxaban, rivaroxaban, and darexaban, all of which target either factor Xa or factor IIa by selective inhibition [26]. Recently, these new oral anticoagulants (NOACs) gained approval for the prevention of VTE after hip arthroplasty or knee arthroplasty planned electively in several European countries.

Unlike traditional anticoagulants, NOACs possess a range of advantages including the absence of food interactions, sporadic drug interactions, shorter onset and offset of action, and the elimination of the urgency for routine laboratory investigative monitoring [28, 29]. However, they have their own limitations such as contraindications or the need to reduce the dose in chronic hepatic and kidney patients.

While, on the other hand, new oral anticoagulants have short have live which can be viewed as both an advantage and a drawback under different instances? For instance, lowering the half-life may make the drug more suitable for emergencies and surgery since it prevents the amount of active ingredient from building up and possible toxicity in the blood, whereas it can be detrimental if the patient forgets to take the medication, potentially putting them at risk [28]. This study revealed that fondaparinux exhibited high efficacy for the prevention of DVT. In its class, Fondaparinux, a synthetic pentasaccharide, is the first of the new generation antithrombotic agents, selective factor Xa inhibitors. Completely absorbed after subcutaneous injection (approximately 700 units/mg) [31], Fondaparinux shows better activity than LMWH (approximately 700 units/mg and 100 units/mg, respectively) [31]. The fact that fondaparinux has a half-life of 17 hours makes it well-suited to be taken once a day.[32] On the other hand, as fondaparinux breaks down in the kidneys, changes in dosage will be needed for patients with poor renal function [31].

Conclusion

This meta-analysis revealed the superior efficacy of apixaban, edoxaban, fondaparinux, and rivaroxaban in preventing deep vein thrombosis after total hip or knee arthroplasty compared to other anticoagulants. However, no significant differences were observed among the agents for pulmonary embolism prevention. These findings highlight the potential benefits of newer oral anticoagulants in optimizing post-surgical outcomes and reducing VTE-associated burden.

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