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Comparison between use of direct oral anticoagulants and aspirin for risk of thromboembolism complications in patients undergoing total knee and hip arthroplasty: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: Total knee and hip arthroplasty are one of the most commonly consistently successful surgeries in orthopedics worldwide. Literature has reported that depending upon the age and co-existing treatments, patients undergoing total knee and hip arthroplasty are often prone to increased risks of developing venous thromboembolic complications. In such cases, chemoprophylaxis with either direct oral anticoagulant therapy with factor-Xa inhibitors (i.e., rivaroxaban, apixaban, dabigatran) and aspirin are widely recommended. Recent surveys suggest that direct oral anticoagulants and aspirin have comparable efficacy. However, there is no consensus in the literature as to which drug is the safest. Therefore, in this review, we shall attempt to evaluate the comparative efficacy between direct oral anticoagulant drugs and aspirin in patients undergoing total joint arthroplasty. To compare risk of venous thromboembolism complications between use of direct oral anticoagulant drugs and aspirin in patients undergoing total knee and hip arthroplasty.

MATERIALS AND METHODS: A sensitive and specific analysis of the literature was performed according to the Cochrane and written according to PRISMA guidelines (Supplementary Table I). Five electronic databases (Web of Science, Embase, CENTRAL, Scopus, and Medline) were evaluated. To compare the efficacy between the drugs we conducted a random-effect meta-analysis according to the outcome (bleeding complications, venous thromboembolism or pulmonary embolism) and overall mortality in patients undergoing total knee and hip arthroplasty.

RESULTS: Overall, 993 studies were found of which 117 had their full texts evaluated. A total of 161,463 patients undergoing total joint arthroplasty with mean age equal 66.2 ± 5.0 years were identified in 14 studies. Higher risks of venous thromboembolism (OR: 1.56 95% CI 1.21-2.01), pulmonary embolism (OR: 1.63, 95% CI: 1.31 -2.04) and overall mortality (OR: 1.35, 95% CI 1.04-1.74) for patients receiving aspirin were verified as compared to direct oral anticoagulant drugs. Subsequently, we further observed that the risks of bleeding complications (OR: 0.89 95% CI 0.67-1.18) were insignificant.

CONCLUSIONS: The study reports higher risks of venous thromboembolism, pulmonary embolism, and overall mortality for the patients receiving aspirin before undergoing total joint arthroplasty.

Key Words:
Arthroplasty, Replacement, Knee, Direct oral anticoagulants, Factor Xa inhibitors, Morbidity, Mortality.

Introduction

Total knee and hip arthroplasty are one of the most successful surgeries in orthopedics in the world[1].

According to the American Society of Hematology, the risk of venous thromboembolism after a knee arthroplasty is aggravated by the following factors: post-surgical transient increase in hypercoagulability; prolonged post-surgical bed rest; previous history of thromboembolism or coexistence of chronic health conditions[2-4]. Incidence between 0.6% to 2.0% of postoperative venous thromboembolism among the patients undergoing hip and knee joint arthroplasty has been observed[5-7]. Venous thromboembolism is

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one of the most common reasons for unplanned hospital readmission and higher postoperative complications[8,9].

Specifically, prophylactic management of patients undergoing a total joint arthroplasty is widely recommended with anticoagulant and antiplatelet drugs (i.e., aspirin) to mitigate the high risks of postoperative venous thromboembolism[4,10]. Direct oral anticoagulant agents including factor Xa inhibitors (i.e., rivaroxaban, apixaban, fondaparinux, edoxaban, betrixaban) as per their class of action are suggested to function primarily by binding selectively to factor X in which eventually inhibits thrombin production by blocking its interaction with its substrate[11,12]. The use of these drugs is also preferred over the warfarin, because of their improved safety profiles and fixed-dose administration[12]. Likewise, antiplatelet agents such as aspirin are reported to act primarily by causing irreversible inhibition of prostaglandin-H synthase (i.e., in the megakaryocytes and platelets) and complete inhibition of cyclooxygenase 1-dependent thromboxane A_2 synthesis causing a reduced vasoconstriction[13]. Although the use of aspirin as a prophylactic agent is largely driven because of its larger availability and cost-effectiveness[14] recent evidence has questioned its implementation as a routine drug for the prevention of venous thromboembolism especially after total knee and hip arthroplasty[15,16].

Few randomized controlled trials[15,17-19] and retrospective cohorts[20-25] had as objective to evaluate the influence of direct oral anticoagulant drugs and of aspirin in morbidity and mortality-related in patients undergoing total knee and hip arthroplasty. However, a lack of consensus exists regarding the outcomes concerning the influence of these drugs on the overall events of venous thromboembolism.

For all we know one systematic review has aimed to comparatively evaluate the prophylactic efficacy between direct oral anticoagulant drugs and aspirin in patients undergoing total knee and hip arthroplasty[26]. Nevertheless, the findings of this review are limited in two important ways. First, it performed comparative analyses on studies only evaluating the prophylactic efficacy between aspirin and rivaroxaban. Therefore, the interpretability of these findings on the other drugs of direct oral anticoagulant's class (i.e., apixaban, dabigatran) is difficult. Secondly, it has failed to include a range of recently published high quality randomized controlled trials[19], and cohort trials[21-24].

Therefore, an updating of the existing state of evidence is strongly warranted. In this systematic review and meta-analysis, we will attempt to bridge the gap in the current state of evidence by evaluating the comparative prophylactic influence between direct oral anticoagulant drugs and aspirin on the overall morbidity and mortality-related aspect in patients undergoing total knee arthroplasty. The findings from this study will help deduce best practice guidelines for clinicians and nursing to effectively modulate thromboembolic outcomes in patients undergoing total knee and hip arthroplasty.

Materials and Methods

We followed the methods describe by Cochrane Handbook and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline (Moher et al[27], 2015) for writing this systematic review and meta-analysis.

Data Search Strategy

The literature search was performed in five electronic scientific databases (Web of Science, Medline, CENTRAL, Embase, and Scopus) from inception until May 30th, 2021. The search was performed across a combination of MeSH terms including "Anticoagulants", "antiplatelets", "rivaroxaban", "apixaban", "dabigatran", "aspirin", "arthroplasty", "joint arthroplasty", "bleeding complication", "venous thromboembolism", "pulmonary embolism", and "mortality". The reference part of the included studies was also manually screened to find any relevant studies. The inclusion criteria were (1) studies evaluating the comparative post-operative outcomes between patients consuming aspirin and factor Xa inhibitors after joint arthroplasty; (2) researches that evaluating the events of venous thromboembolism, pulmonary embolism, bleeding complications, and overall mortality in patients undergoing knee arthroplasty; (3) studies realized in human participants; (4) studies with design of randomized controlled trials, case-control, prospective or retrospective cohort; (5) studies published in peer-reviewed scientific journals.

The studies were independently screened by two different reviewers. In the situation of disagreement discussions with a third reviewer was conducted.

Quality Assessment

The risk of bias was done by Cochrane's risk of bias assessment tool for randomized controlled trials[28]. This tool evaluates the outcomes for selective reporting, confounding bias, measurement of outcomes, and incomplete data availability as threats that can instigate instigating. For cohort studies the risk of bias was supported by Newcastle Ottawa scale[29]. This tool evaluates the outcomes for selective reporting, confounding bias, measurement of outcomes, and incomplete data availability as threats that can instigate instigating.

The methodological quality was performed independently by two reviewers and in case of disagreements a third reviewer intervened to arbitrate.

Data Analysis

Statistical evaluations were performed using Comprehensive Meta-Analysis software version 2.0[30]. Meta-analysis of proportions was carried out using double arcsine transformation and normalization of presented data. In addition, utilizing the quality effects models approach (QE), pooled proportions and 95% confidence intervals (CI) were calculated as the random effect model is not statistically adequate to analyze high heterogeneity data[31]. We computed the odds ratio to two groups of drugs. Heterogeneity was assessed by Cochrane's Q test considering a statistically significant value for $p < 0.1$, and Higgins $I^2 \geq 25\%$ and <75% as moderate heterogeneity and ≥75% of substantial heterogeneity[32]. Subgroup analyses were evaluated to examine the potential sources of between-study heterogeneity. In case there are fewer than 10 studies in a meta-analysis, we constructed a funnel plot to investigate the potential for publication bias for the primary outcome by visual inspection for asymmetry. Duval and Tweedie's trim and fill analysis were conducted if the publication bias becomes evident[33]. The publication bias was characterized by the imputation of studies from either side of the plotted graph to identify any unbiased effect. The significance level for this review was determined at 5%.

Results

Overall, 993 studies were found of which 117 had their full texts evaluated. A total of 161,463 patients undergoing total joint and hip arthroplasty with mean age equal 66.2 ± 5.0 years were identified in 14 studies. Five of the included studies[15,17-19,34] were randomized controlled trials, nine were retrospective cohort studies[20-25,35-37]. The data were extracted and summarized in Table I. After detailed analysis, 14 individual studies (trials and cohort studies) met the inclusion criteria, and all of them reported adequate data to be meta-analyzed.

Participant Information

Data from a total of 161,463 (161,463w, 66428M) patients were included in 14 studies (Figure 1). A total of 84779 (49353w, 35113M) patients received aspirin, and 76684 (45027w, 31315M) patients received direct oral anticoagulants. Three studies[18,23,37] did not define the sex distribution of their sample.

The mean age of the participants was 66.2 ± 5.1 years old and the groups were 66.3 ± 4.6 years for patients receiving aspirin and 66.0 ± 5.6 years for patients receiving direct anticoagulants was 66.0 ± 5.6 years. Three studies[24,35,37] did not report the age of their sample.

Quality Assessment for Randomized Controlled Trials Studies

We analyzed the risk of bias in the methodology of the randomized controlled trials with Cochrane's risk of bias assessment tool for randomized controlled trials and the results of this tool have been demonstrated in Table II. The overall risk in the included studies was low. We observed that allocation of concealment, blinding of outcome assessment and other biases were the aspects for which bias was observed within most of the included studies (Table II).

Quality Assessment for Cohort Studies

The overall risk was found to be low in the cohort studies. The overall risk of bias has also been demonstrated in Table III.

Publication Bias

We used Duval and Tweedy's trim and fill method to determine missing studies according to the random effect model on either side of the mean effect of the funnel plot. The method observed that three studies were missing on the right side of the mean effect. The overall random effect models determined the point estimates and the 95% confidence intervals for all the combined studies as 1.56 (95% CI 1.21-2.01), after using the trim and fill the imputed point estimates were estimated as 1.62 (95% CI: 1.25-2.10). The publication bias is reported in Figure 2.

Table I. Characteristics of included studies in systematic review.

Reference	Country	Type of study	Sample descriptive by sex	Age (mean ± S.D in years-old)	Type of surgery	Follow-up (days)	Venous thromboembolism (n)	Pulmonary embolism (n)	Bleeding complication (n)	Mortality (n)
Ren et al[19] (2021)	China	Randomized controlled trial	Aspirin: 34 (21W, 13M) Factor Xa inhibitor: 36 (25W, 11M)	Aspirin: 54.5 Factor Xa inhibitor: 50	THA Factor Xa inhibitor: 3	90	Aspirin: 3 Factor Xa inhibitor: 3	–	Aspirin: 1 Factor Xa inhibitor: 3	–
Matharu et al[22] (2020)	UK	Retrospective cohort study	TKA Aspirin: 42590 (24059W, 18531M) Factor Xa inhibitor: 30697 (17362W, 3335M) THA Aspirin: 35904 (21773W, 14131M) Factor Xa inhibitor: 29522 (17883W,	TKA Aspirin: 70.2 ± 9.2 Factor Xa inhibitor: 69.9 ± 9.1 THA Aspirin: 69.5 ± 10.5 Factor Xa inhibitor: 69.2 ± 10.4	TKA, THA	NI	TKA Aspirin: 160 Factor Xa inhibitor: 72 THA Aspirin: 226 Factor Xa inhibitor: 102	TKA Aspirin: 168 Factor Xa inhibitor: 79 THA Aspirin: 107 Factor Xa inhibitor: 54	TKA Aspirin: 76 Factor Xa inhibitor: 46 THA Aspirin: 42 Factor Xa inhibitor: 32	TKA Aspirin: 64 Factor Xa inhibitor: 27 THA Aspirin: 95 Factor Xa inhibitor: 63
Kim et al[21] (2019)	South Korea	Retrospective cohort study	Aspirin: 2071 (1215W, 856M) Factor Xa inhibitor: 2071 (1234W, 837M)	Aspirin: 66.2 ± 15.8 Factor Xa inhibitor: 65.5 ± 15.2	THA	90	Aspirin: 33 Factor Xa inhibitor: 12	–	Aspirin: 43 Factor Xa inhibitor: 39	–

Continued

Table I ***(Continued).*** Characteristics of included studies in systematic review.

Reference	Country	Type of study	Sample descriptive by sex	Age (mean ± S.D in years-old)	Type of surgery	Follow-up (days)	Venous thromboembolism (n)	Pulmonary embolism (n)	Bleeding complication (n)	Mortality (n)
McHale et al[23] (2019)	UK	Retrospective cohort study	TKA Aspirin: 95 Factor Xa inhibitor: 123	TKA Aspirin: 71.5 ± 9.4 Factor Xa THA Aspirin: 110 Factor Xa inhibitor: 139	TKA, THA inhibitor: 71.5 ± 10.8 THA Aspirin: 70.4 ± 11.1 Factor Xa inhibitor: 7 1.8 ± 11.1	90	TKA Aspirin: 0 Factor Xa inhibitor: 2	TKA Aspirin: 0 Factor Xa inhibitor: 1 THA Aspirin: 0 Factor Xa inhibitor: 3	–	TKA Aspirin: 0 Factor Xa inhibitor: 2 THA Aspirin: 0 Factor Xa inhibitor: 1
Richardson et al[24] (2019)	USA	Retrospective cohort study	Aspirin: 548 (334W, 214M) Factor Xa inhibitor: 6524 (3958W, 2566)	49->90	TKA	90	Aspirin: 16 Factor Xa inhibitor: 110	Aspirin: 11 Factor Xa inhibitor: 37	–	–
Yuenyongviwat et al[25] (2019)	Thailand	Retrospective cohort study	Aspirin: 79 (69W, 10M) Factor Xa inhibitor: 76 (67W, 9M)	Aspirin: 70.0 ± 5.2 Factor Xa inhibitor: 71.4 ± 6.1	TKA	42	Aspirin: 0 Factor Xa inhibitor: 0	Aspirin: 0 Factor Xa inhibitor: 0	Aspirin: 0 Factor Xa inhibitor: 0	–
Colleoni et al15 (2018)	Brazil	Randomized controlled trial	Aspirin: 14 (13W, 1M) Factor Xa inhibitor: 18 (14W, 4M)	Aspirin: 71.2 ± 6.3 Factor Xa inhibitor: 67.1 ± 7.6	TKA	90	Aspirin: 1 Factor Xa inhibitor: 2	–	Aspirin: 1 Factor X inhibitor: 0	Aspirin: 0 Factor X inhibitor: 0 1

Continued

Table I *(Continued)*. Characteristics of included studies in systematic review.

Reference	Country	Type of study	Sample descriptive by sex	Age (mean ± S.D in years-old)	Type of surgery	Follow-up (days)	Venous thromboembolism (n)	Pulmonary embolism (n)	Bleeding complication (n)	Mortality (n)
Anderson et al17 (2018)	Canada	Randomized controlled trial	TKA Aspirin: 805 TKA Factor Xa inhibitor: 815 THA Aspirin: 902 Factor Xa inhibitor: 902	TKA Aspirin: 64.6 ± 8.7 (487W, 318M) Factor Xa inhibitor: 64.7 ± 8.4 (462W, 353M) THA Aspirin: 61.3 ± 11.1 (416W, 486M) Factor Xa inhibitor: 60.9 ± 11.0 (422W, 480M)	TKA, THA	90	TKA Aspirin: 7 Factor Xa inhibitor: 7 THA Aspirin: 4 Factor Xa inhibitor: 5	TKA Aspirin: 3 Factor Xa inhibitor: 4 THA Aspirin: 2 Factor Xa inhibitor: 2	TKA Aspirin: 11 Factor Xa inhibitor: 10 THA Aspirin: 11 Factor Xa inhibitor: 7	TKA Aspirin: 1 Factor Xa inhibitor: 0 THA Aspirin: 0 Factor Xa inhibitor: 0
Lindquist et al[36] (2018)	USA	Retrospective cohort study	Aspirin: 366 (223W, 143M) Factor Xa inhibitor: 440 (285W, 182M)	Aspirin: 65.8 Factor Xa inhibitor: 65.4	TKA, THA	30	–	–	Aspirin: 11 Factor Xa inhibitor: 30	–
Garfinkel et al[20] (2018)	USA	Retrospective cohort study	Aspirin: 27 (16W, 11M) Factor Xa inhibitor: 32 (20W, 12M)	Aspirin: 62.8 Aspirin: 0 Factor Xa inhibitor: 69.3	TKA, THA	270	Aspirin: 0 Factor Xa inhibitor: 0	–	Aspirin: 0 Factor Xa inhibitor: 1	–

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Table I *(Continued)*. Characteristics of included studies in systematic review.

Reference	Country	Type of study	Sample descriptive by sex	Age (mean ± S.D in years-old)	Type of surgery	Follow-up (days)	Venous thromboembolism (n)	Pulmonary embolism (n)	Bleeding complication (n)	Mortality (n)
Bala et al[35] (2017)	USA	Retrospective cohort study	Aspirin: 1016 (645W, 371M) Factor Xa inhibitor: 5.080 (3.225W, 1.855M)	45-84	TKA	90	Aspirin: 30 Factor Xa inhibitor: 149	Aspirin: 12 Factor Xa inhibitor: 45	Aspirin: 12 Factor Xa inhibitor: 70	–
Miao et al[37] (2015)	China	Retrospective cohort study	Aspirin: 48 Factor Xa inhibitor: 47	48-76	TKA	NI	Aspirin: 5 Factor Xa inhibitor: 3	Aspirin: 1 Factor Xa inhibitor: 0	Aspirin: 2 Factor Xa inhibitor: 11	–
Jiang et al[18] (2014)	China	Randomized controlled trial	Aspirin: 60 Factor Xa inhibitor: 60	Aspirin: 65.1 ± 7.5 Factor Xa	TKA	42	Aspirin: 0 Factor Xa inhibitor: 0	–	Aspirin: 1 Factor Xa inhibitor: 2	Aspirin: 0 Factor Xa inhibitor: 0
Zou et al[34] (2014)	China	Randomized controlled trial	Aspirin: 110 (82W, 28M) Factor Xa inhibitor: 102 (70W, 32M)	Aspirin: 62.7 Factor Xa inhibitor: 63.5	TKA	28	Aspirin: 18 Factor Xa inhibitor: 3	–	Aspirin: 2 Factor Xa inhibitor: 5	

M: Mean: S.D: Standard deviation, TKA: Total knee arthroplasty, THA: Total hip arthroplasty; NI: Not informed; W-woman; M-men.

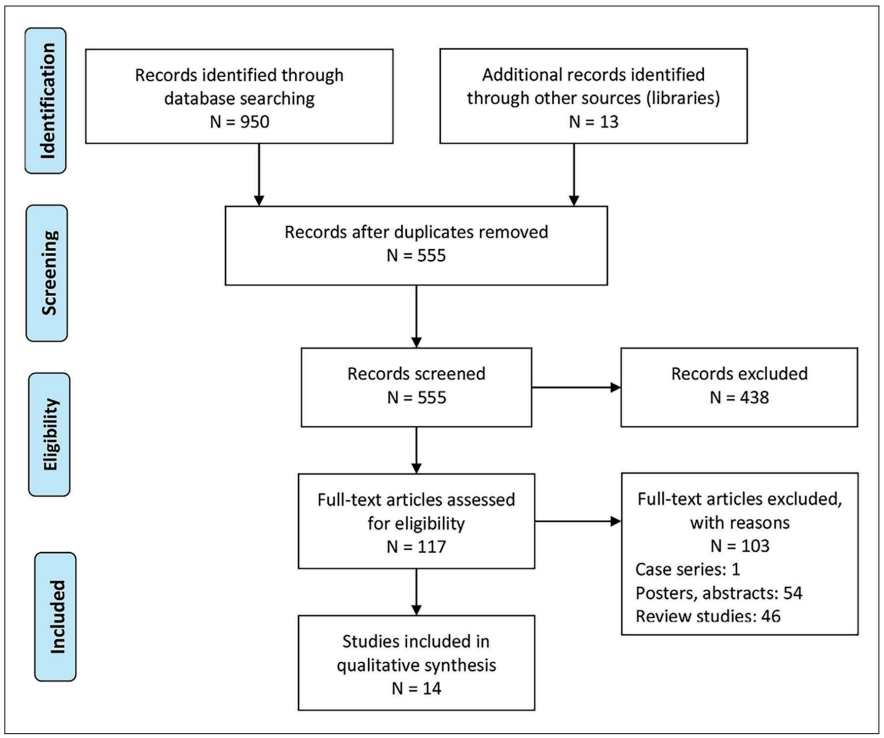

Figure 1. Illustrating the PRISMA flowchart.

Meta-Analysis Report

Venous Thromboembolism

The venous thromboembolism in patients receiving direct oral anticoagulant drugs and aspirin was evaluated at 10 studies[15,1719,21-24,34,35,37]. We observed an increased odds ratio (OR) suggesting higher risks of venous thromboembolism for patients receiving aspirin as compared to direct oral anticoagulants (Figure 3) (OR: 1.56, 95% C.I: 1.21-2.01, p =0.001), with negligible heterogeneity (I^2: 14.1%).

Pulmonary Embolism

The pulmonary embolism in patients receiving direct oral anticoagulant drugs and aspirin was reported by six studies[17,22,23,24,35,37]. We observed an increased OR suggesting a higher risk of pulmonary embolism for patients receiving aspirin as compared to direct oral anticoagulants (Figure 4) (OR: 1.63, 95% C.I: 1.31-2.04, p<0.001), with negligible heterogeneity (I^2: 3.1%).

Bleeding Complication

The bleeding complications in patients receiving direct oral anticoagulant drugs and aspi-

Table II. Risk of Bias of randomized controlled trials included in this systematic review.

Reference	Random sequence generation	Allocation concealment	Selective reporting	Other bias	Blinding of participants & personnel	Blinding of outcome assessment	Incomplete outcome data
Ren et al[19] (2021)	+	?	+	-	+	?	+
Colleoni et al[15] (2018)	+	?	+	-	+	?	+
Anderson et al[17] (2018)	+	+	+	?	+	+	+
Jiang et al[18] (2014)	+	?	+	-	+	?	+
Zou et al[34] (2014)	+	+	+	+	+	+	+

Table III. Risk of bias for individual studies based on the Newcastle Ottawa scale.

Study	Selection				Comparability		Outcome			Tota (9/9)
	Representative of the exposed cohort	Selection of external cohort	Ascertainment of exposure	Outcome of interest does not present at start	Main factor	Additional factor	Assessment of outcome	Sufficient follow up	Adequacy of follow up	
Matharu et al[22] (2020)	+	+	0	+	+	+	0	+	+	7
Kim et al[21] (2019)	+	+	0	0	0	+	0	+	+	5
McHale et al[23] (2019)	+	+	0	+	+	+	0	+	+	7
Richardson et al[24] (2019)	+	+	0	0	+	+	0	+	+	6
Yuenyongviwat et al[25] (2019)	+	+	0	+	+	+	0	+	+	7
Lindquist et al[36] (2018)	+	+	0	0	+	+	0	+	+	6
Garfinkel et al[20] (2018)	+	+	0	0	0	+	0	+	+	5
Bala et al[35] (2017)	+	+	0	0	+	+	0	+	+	6
Miao et al[37] (2015)	+	+	0	0	+	+	0	+	+	6

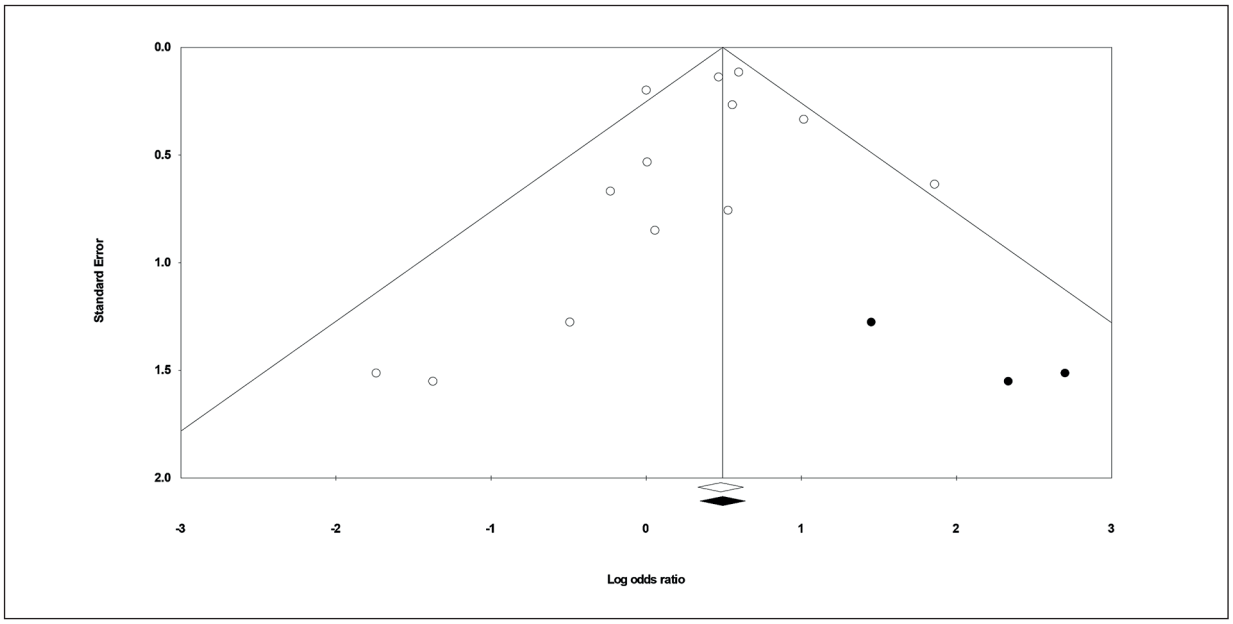

Figure 2. Publication bias evaluated by Duval & Tweedy's trim and fill method.

rin were reported in eleven studies[15,17-21,34-37]. We observed a decreased OR suggesting a higher risk of bleeding complications for patients receiving direct oral anticoagulants as compared to aspirin (Figure 5) (OR: 0.89, 95% C.I: 0.67-1.18, p =0.440), with negligible heterogeneity (I^2: 9.70%).

Mortality

The total mortality in patients receiving direct oral anticoagulant drugs was reported by four studies[15,17,22,23]. We observed an increased OR suggesting a higher risk of mortality for patients receiving direct oral anticoagulants as compared to aspirin (Figure 6) (OR: 1.35, 95%

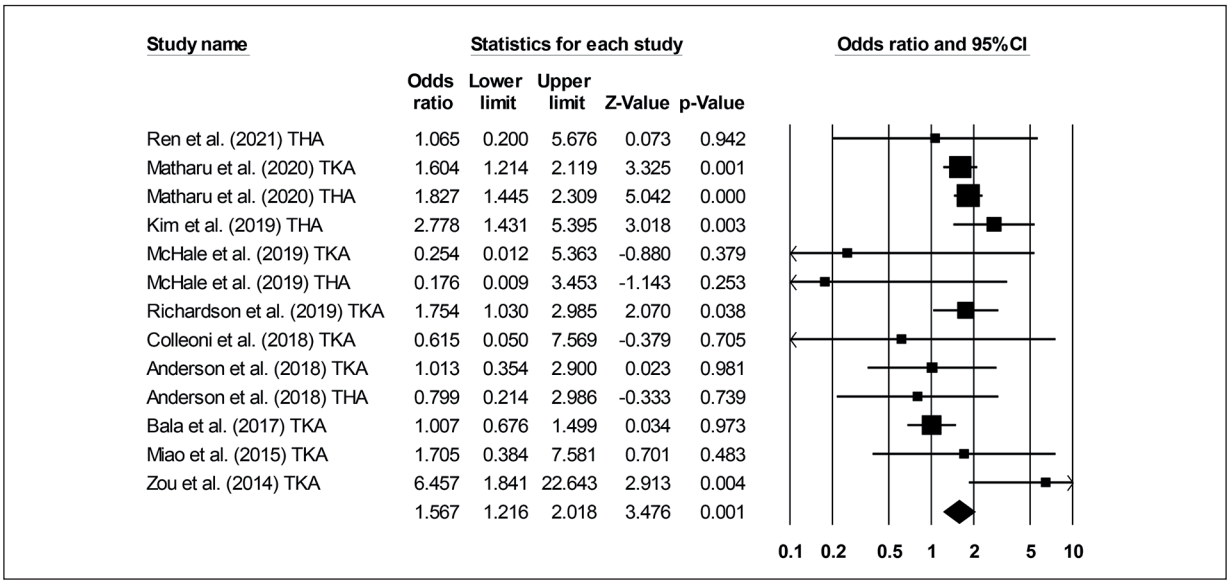

Figure 3. Forest plot for studies evaluating venous thromboembolism in patients receiving aspirin or factor Xa inhibitors after total joint arthroplasty. The odds ratio is presented as black boxes whereas 95% confidence intervals are presented as whiskers. A reduced odds ratio represents higher risks of venous thromboembolism in patients receiving factor Xa inhibitors and a positive odds ratio represents higher risks of venous thromboembolism in patients receiving aspirin (TKA: total knee arthroplasty, THA: total hip arthroplasty).

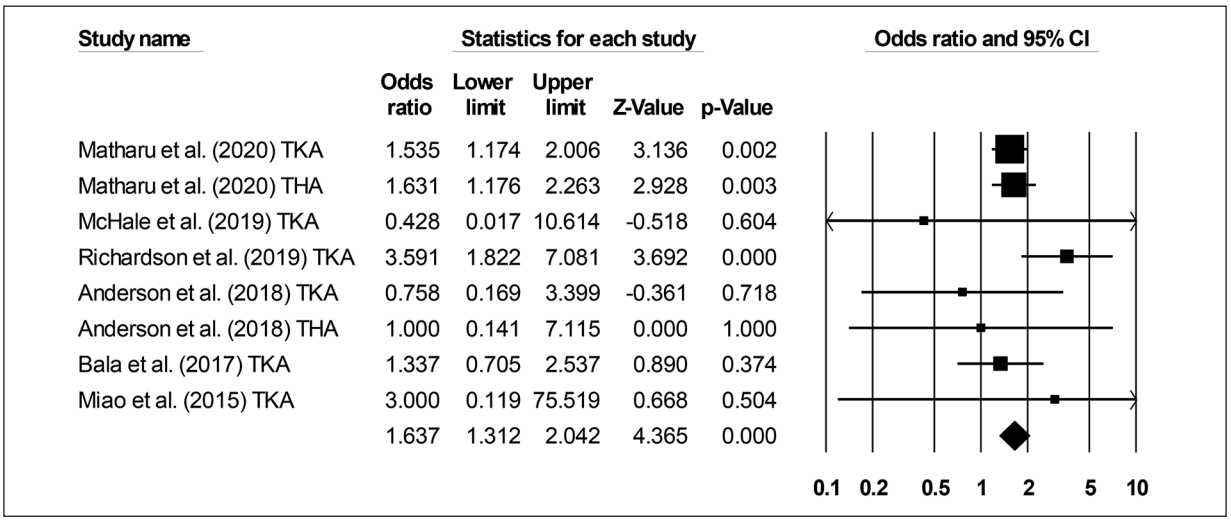

Figure 4. Forest plot for studies evaluating the risks of pulmonary embolism in patients receiving aspirin or factor Xa inhibitors after total joint arthroplasty. The odds ratio is presented as black boxes whereas 95% confidence intervals are presented as whiskers. A reduced odds ratio represents higher risks of pulmonary embolism in patients receiving factor Xa inhibitors and a positive odds ratio represents higher risks of pulmonary embolism in patients receiving aspirin (TKA: total knee arthroplasty, THA: total hip arthroplasty).

C.I: 1.04- 1.74, p =0.02) with no heterogeneity (I^2: 0.00%).

Discussion

In this systematic review and meta-analysis was observed a significantly higher risk of venous thromboembolism, pulmonary embolism, and overall mortality for the patients receiving aspirin when compared patients receiving direct oral anticoagulants before total knee and hip joint arthroplasty.

Studies have widely reported a high incidence of venous thromboembolism especially after low-

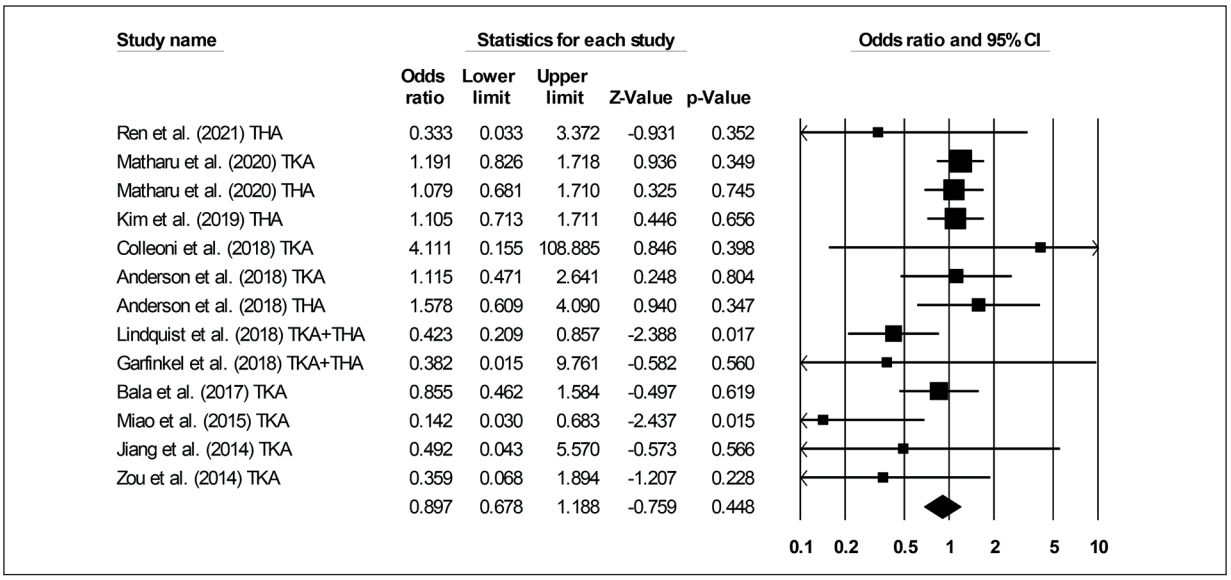

Figure 5. Forest plot for studies evaluating the risks of bleeding complications in patients receiving aspirin or factor Xa inhibitors after total joint arthroplasty. The odds ratio is presented as black boxes whereas 95% confidence intervals are presented as whiskers. A reduced odds ratio represents higher risks of bleeding complications in patients receiving factor Xa inhibitors and a positive odds ratio represents higher risks of bleeding complications in patients receiving aspirin (TKA: total knee arthroplasty, THA: total hip arthroplasty).

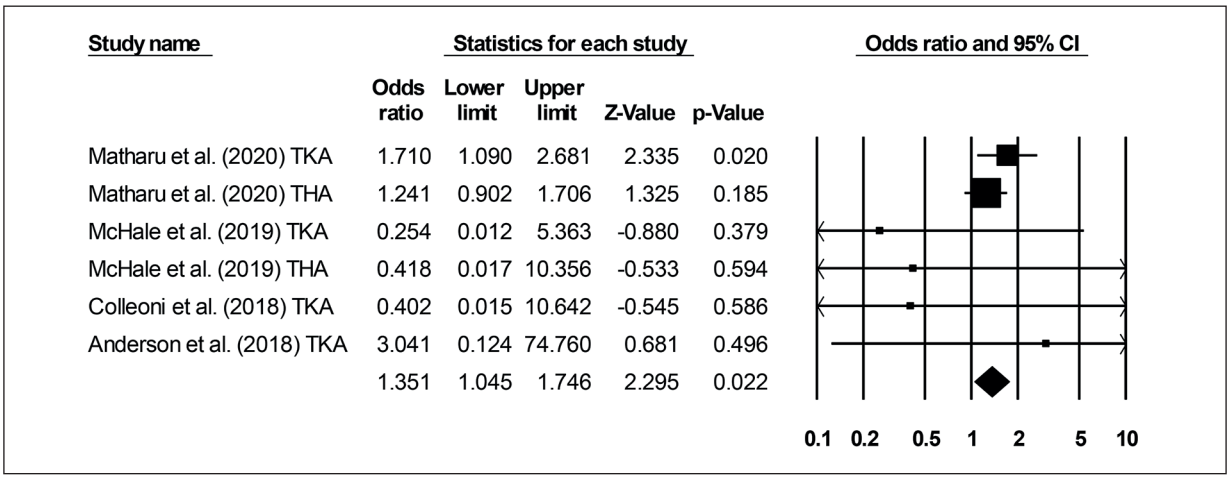

Figure 6. Forest plot for studies evaluating the risks of overall mortality in patients receiving aspirin or factor Xa inhibitors after total joint arthroplasty. (TKA: total knee arthroplasty, THA: total hip arthroplasty).

er limb joint arthroplasties (i.e., total knee and hip arthroplasties)[2,4]. Fisher (2011)[38] attributed the pathogenesis for the increased incidence of venous thromboembolism after joint arthroplasty to onset of Virchow's triad hypothesized that perhaps an inadvertent trauma to the soft tissue (i.e., vascular structures) during the radical procedure might aggravate coagulation due to excess production of thrombin. The mechanical resection of the bone marrow during the procedure might also dislodge parts of marrow in the circulation ultimately precipitating the onset of venous thromboembolism[38]. To manage this increased risk of venous thromboembolism, direct oral anticoagulant drugs (i.e., factor Xa inhibitors) and antiplatelet drugs (i.e., aspirin) are commonly prescribed to the patients undergoing total joint arthroplasty[39]. Recent studies have suggested that the administration of these direct oral anticoagulants is superior in terms of improving not only the morbidity outcomes but also reduce the overall mortality burden in patients undergoing total joint and hip arthroplasty[21,22,24,34]. Despite surplus evidence suggesting the beneficial influence of direct oral anticoagulants over aspirin for managing venous thromboembolism, a consensus in terms of direct oral anticoagulant's efficacy for improving morbidity and mortality outcomes post total joint and hip arthroplasty is missing.

In this research, it was observed that included studies had reported a differential prophylactic outcome between direct oral anticoagulants and aspirin in terms of reducing the events of venous thromboembolism and pulmonary embolism. On the other hand, Matharu et al (2020)[22] in retrospective cohort observed significant reduction in incidence of venous thromboembolism in patients receiving direct oral anticoagulants as compared to aspirin for both knee joint (direct oral anticoagulant: 0.49% *vs.* aspirin: 0.68%) and hip joint arthroplasty (0.37% *vs.* 0.59%). The authors also reported a reduction in incidence of pulmonary embolism with direct oral anticoagulants as well for patients undergoing both knee (0.26% *vs.* 0.39%) and hip (0.18% *vs.* 0.30%) joint and hip arthroplasty. Similarly, studies[21,24,35] have also reported higher events of venous thromboembolism in patients receiving aspirin and that contrary to the conventional notion that direct oral anticoagulants have a poorer safety profile[40], direct oral anticoagulant drugs in their large cohort did not account for a longer duration of hospital stay or readmission as compared to the group consuming aspirin. On the other hand, McHale et al (2019)[23] observed that patients consuming dabigatran as a prophylactic agent observed higher events of venous thromboembolism as compared to aspirin (total hip arthroplasty: 2.15% *vs.* 0.00%, total knee arthroplasty: 1.62% *vs.* 0.00%). The authors, however, cautioned of possible bias in their results perhaps due to either the observational nature of their study and/or due to medical error by surgeons in their study who wrongly prescribed dabigatran. In our present meta-analysis, we nonetheless support the findings of the former and report significantly higher risks of both venous thromboembolism (OR: 1.56, CI 95%, p: 0.001) and pulmonary embolism (OR:1.63,CI 95%, p <0.001) in patients receiving prophylaxis

by aspirin as compared to direct oral anticoagulants in patients undergoing total joint arthroplasty.

Besides, we also attempted to develop a consensus regarding the prophylactic impact of these drugs on the risks of bleeding complications and overall mortality outcomes in patients undergoing total joint arthroplasty. Firstly, we observed in our meta-analysis that direct oral anticoagulant drugs accounted for insignificantly higher incidence (0.89, p =0.440) of bleeding complications as compared to aspirin in patients undergoing total joint arthroplasty. Garfinkel et al (2018)[20] for instance reported higher events of bleeding complications for patients receiving direct oral anticoagulant prophylaxis as compared to aspirin. The authors reported that delayed wound healing was the most commonly occurring complication for patients receiving direct oral anticoagulants, followed by hematoma and postoperative cellulitis. In our opinion, we presume that one important factor that could have influenced the result of Garfinkel et al (2018)[20] is the differential age and body mass index distribution of their cohort receiving direct oral anticoagulants (i.e. mean age: 69.3 years, BMI: 29.4 kg/m^2) as compared to aspirin (i.e. 62.8 years, BMI: 26.9 kg/m^2). Similarly, Ren et al (2021)[19] , Miao et al (2015)[37], and Zou et al (2014)[34] too reported similar outcomes in terms of higher risks of bleeding complications in the cohort receiving direct oral anticoagulant prophylaxis as compared to aspirin. In terms of overall mortality, on the contrary, we observed that patients receiving prophylactic aspirin had significantly higher risks (OR:1.35, 95% CI, p =0.020) of overall mortality as compared to patients receiving direct oral anticoagulants. Matharu et al (2020)[22] reported higher risks of overall mortality in patients receiving aspirin prophylaxis as compared to direct oral anticoagulants for both hip joint (aspirin: 0.26% *vs.* direct oral anticoagulant: 0.21%) and knee joint (0.15% *vs.* 0.09%) arthroplasty. This reduced fatality outcomes for direct oral anticoagulants could perhaps be attributed to the findings of Chai-Adisaksopha et al (2015)[41] and Frenkel Rutenberg et al (2018)[42] in which reduced events of intracranial bleeding with direct oral anticoagulants have been documented.

Despite being a novel study, few limitations existed in the present systematic review and meta-analysis. Primarily,–we observed different follow-up in studies included in this review (see Table I, Ren et al[19] 90 days, Garfinkel et al[20] 270 days). This factor could be an important source of heterogeneity in the analyses we conducted and could possibly incur bias in our results. For this, we therefore strongly recommend future studies to address this limitation by replicating these findings in multi-center randomized controlled trials. The evaluation of these outcomes would be highly beneficial for orthopedic surgeons and nursing staff alike to determine best practice guidelines to reduce post-operative thromboembolic complications associated with total joint and hip arthroplasty.

Conclusions

In conclusion, we provide preliminary evidence regarding the stronger negative influence of aspirin on the outcome of venous thromboembolism, pulmonary embolism, and overall mortality in patients undergoing total joint and hip arthroplasty. We also provide evidence regarding slightly higher events of bleeding complications for the patients receiving direct oral anticoagulant drugs as compared to aspirin. This finding can have implications in developing best practice guidelines for reducing postoperative thromboembolic complications in patients undergoing total joint and hip arthroplasty.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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