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Systematic Review and Meta-Analysis

Low-Dose Aspirin Is Adequate for Venous Thromboembolism Prevention Following Total Joint Arthroplasty: A Systematic Review

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ABSTRACT

Background: Patients undergoing total joint arthroplasty (TJA) are at risk of developing venous thromboembolism (VTE) without adequate prophylaxis. Since the American Academy of Orthopedic Surgeons issued guidelines in 2007 recommending aspirin 325 mg bis in die for 6 weeks, aspirin has been favored as the main VTE prophylaxis. However, the appropriate dose and duration of aspirin are not well-studied. This systematic review aims to identify any differences between high and low dose as well as duration for aspirin thromboprophylaxis after TJA as outlined by previous studies.

Methods: A search was performed using Ovid MEDLINE, EMBASE, and PubMed, including articles up to July 2016. Studies were included if they contained at least 1 cohort that underwent TJA with aspirin as the sole chemoprophylaxis and reported either (1) symptomatic VTE or (2) secondary outcomes such as major bleeding or 90-day mortality.

Results: Forty-five papers were included. There were no significant differences in symptomatic pulmonary embolism, symptomatic deep vein thrombosis, 90-day mortality, or major bleeding between patients receiving low-dose or high-dose aspirin. Patients treated with aspirin for <4 weeks had a higher risk of major bleeding (1.59%) vs patients treated for 4 weeks (0.15%), which may be attributed to premature cessation or differential reporting. Patients treated with aspirin for <4 weeks had a statistically higher 90-day mortality (1.95%) vs patients treated for 4 weeks (0.07%). There was no significant difference between incidence of pulmonary embolism or deep vein thrombosis and the durations of aspirin treatment.

Conclusion: This review suggests that low-dose aspirin is not inferior to high-dose aspirin for VTE thromboprophylaxis in TJA patients. Additionally, patients treated with aspirin for less than 4 weeks may have a higher risk of major bleeding and 90-day mortality compared to patients treated for a longer duration.

Patients undergoing total joint arthroplasty (TJA) have increased rates of venous thromboembolism (VTE), which can be reduced by administration of thromboprophylaxis [1]. Although guidelines exist for thromboprophylaxis after TJA, the efficacy and safety of different modalities still remains controversial [1–3]. Aspirin is now considered safe and effective for VTE prevention for total hip (THA) [4,5] and total knee arthroplasty (TKA) [6,7] with low incidences of major bleeding, low costs [8], and low risk of infection [9].

The American College of Chest Physicians (ACCP) currently recommends aspirin for 10-14 days after orthopedic surgery and enables an extended treatment of up to 35 days [10]. In 2007, the American Academy of Orthopedic Surgeons (AAOS) issued a guideline recommending aspirin prophylaxis 325 mg bis in die (BID) for 6 weeks for VTE prevention after TJA for patients at standard risk of pulmonary embolism (PE) and major bleeding, standard risk of PE and elevated risk of major bleeding, and elevated risk of PE and major bleeding groups separately [11]. This regime has been followed by many surgeons since the guidelines were released. However, recent studies have shown adequate thromboprophylaxis at the lower daily doses of aspirin [12].

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Aspirin has been shown to have less major bleeding after TJA compared to other more aggressive anticoagulants [13]. Previous studies have shown that aspirin has a lower rate of symptomatic PE and deep vein thrombosis (DVT) [2,14], lower major bleeding rates [6,15], reduced perioperative mortality [16], and fewer wound complications [17] compared to warfarin. Recent recommendations from the National Institutes for Clinical Excellence [18] and European VTE guidelines taskforce [19] also advocate its usage for chemoprophylaxis after elective joint arthroplasty.

It is important to determine the adequate dose and duration of aspirin thromboprophylaxis in order to successfully prevent VTE after TJA, while decreasing negative risks such as major bleeding and 90-day mortality. To our knowledge, there is no systematic review published in the literature analyzing low-dose vs high-dose aspirin as well as investigating duration of aspirin for thromboprophylaxis after TJA. A prior systematic review published in 2016 investigated aspirin as a thromboprophylactic agent and found that aspirin alone and in multimodal approaches had a low incidence of VTE after hip and knee arthroplasty [20]. However, this study did not investigate the optimal dose and duration of aspirin, which are both critical factors for thromboprophylaxis.

The purpose of this systematic review is thus to determine any differences between high and low dose and duration of aspirin for patients undergoing THA and TKA from the literature, and also compare pertinent outcomes when aspirin vs warfarin was administered.

Materials and Methods

Electronic literature search was performed using Ovid MEDLINE, PubMed, and EMBASE. Search of these databases was carried out in accordance with the Cochrane Collaboration, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and Meta-analysis of observational Studies in Epidemiology (MOOSE) recommendations [21]. To achieve the maximum sensitivity of the search strategy, the terms "knee arthroplasty OR hip arthroplasty OR THA OR TKA OR TJA OR total knee replacement" were combined with "venous thromboembolism prophylaxis OR aspirin" and were used as Medical Subject Headings terms. Duplicate studies were removed. Titles and abstracts were manually scanned by 2 independent researchers in accordance with our inclusion criteria.

Studies were included if they reported at least 1 cohort that underwent TJA with aspirin as the sole chemoprophylaxis and was (1) published in the English language between 2000 and 2016, (2) included patients undergoing TKA or THA, and reported either (3) symptomatic VTE or (4) secondary outcomes including major bleeding or mortality, (5) minimum follow-up of 90 days. We included all levels of evidence. Asymptomatic VTE identified by screening scans were not included. We incorporated all original studies in our initial search; however, abstracts, case reports, conference presentations, editorials, reviews, studies with pooled trials, experimental studies, and expert opinions were excluded.

The incidence of symptomatic PE/DVT, 90-day mortality, and major bleeding (defined as gastrointestinal (GI) bleeding, intracranial bleeding, requiring 2 or more units of transfusion, or hematoma requiring return to the operating room) were collected for aspirin and warfarin. Daily dose and duration were collected for aspirin only. Minor bleeding and postoperative transfusion were excluded from the analysis as these variables were not consistently collected throughout the reviewed literature. Additionally, study characteristics (year of publication, design, total number of patients, level of evidence), length of follow-up, and type of surgery (primary vs revision, THA vs TKA) were obtained from each included full-text article.

Statistical Analysis

We used a generalized linear mixed model with dose and duration as the fixed effect and each study as the randomized effect. We ran each model twice with dose alone and once with dose and duration. We created 3 categories for dose: <162 mg of aspirin daily as low dose, >162 mg of aspirin daily as high dose, and warfarin. For the duration of aspirin prophylaxis we also defined 3 categories (<4 weeks, 4 weeks, and >4 weeks). After controlling for high-dose vs low-dose aspirin, we ran the duration for each category of aspirin. *P*-values <.05 were considered statistically significant.

Results

We identified 1918 papers in our initial electronic search (Figure 1). There were 1668 papers remaining after the duplicates were removed. After reviewing titles and abstracts according to our specific criteria, 88 full-text articles were reviewed. Following careful evaluation of the 88 studies, 43 studies were excluded (Figure 1). Ultimately, 45 studies were included in this systematic review [3–7,15,22–59].

Nine studies (20%) included patients receiving aspirin <162 mg/d and 37 studies (80%) included a dose >162 mg/d (1 study included both low-dose and high-dose aspirin). Seven studies administered aspirin for <4 weeks, 7 studies administered aspirin for a duration of 4 weeks, and 16 studies gave a duration of >4 weeks. Fifteen papers included comparative data for patients who received warfarin vs patients receiving aspirin. There were 6 level I studies, 4 level II studies, 18 level III studies, and 17 level IV studies.

Low-Dose Aspirin vs High-Dose Aspirin

There were no significant differences in symptomatic PE, symptomatic DVT, 90-day mortality, or major bleeding between

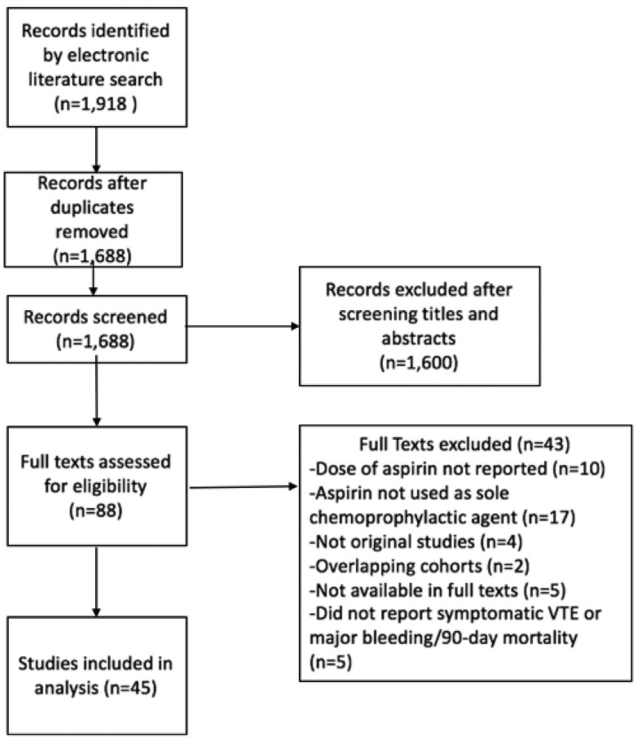

Fig. 1. Screening and PRISMA study selection in this systematic review. VTE, venous thromboembolism.

Table 1
Effect of Low Dose Aspirin, High Dose Aspirin, and Warfarin on the Incidence of Symptomatic PE, DVT, 90-D Mortality, and Major Bleeding.

Outcome	Low Dose Aspirin[a]	High Dose Aspirin	*P*-Value	Warfarin	*P*-Value
Symptomatic PE	0.33% (0.1-0.8)	0.65% (0.5-0.9)	.161	1.24% (0.8-2.0)	**.008**
Symptomatic DVT	0.52% (0.2-1.5)	0.99% (0.6-1.6)	.233	1.68% (1.1-2.8)	**.035**
90-D mortality	0.33% (0.2-0.7)	0.21% (0.1-0.4)	.190	0.42% (0.2-0.8)	.410
Major bleeding	0.54% (0.2-2.0)	0.29% (0.2-0.5)	.376	0.46% (0.2-1.0)	.836

Data are presented as percentage of outcome with 95% confidence intervals in parentheses. Bold *P*-values indicate a statistically significant value.
PE, pulmonary embolism; DVT, deep vein thrombosis.
[a] Comparison/reference group.

patients receiving low-dose or high-dose aspirin (Table 1). The incidence of symptomatic PE of 0.33% (95% confidence interval [CI] 0.1-0.8) in the low-dose group was not significantly different from the 0.65% (95% CI 0.5-0.9) in the high-dose group ($P = .161$). The incidence of symptomatic DVT of 0.52% (95% CI 0.2-1.5) in the low-dose group was not significantly different from the 0.99% (95% CI 0.6-1.6) in the high-dose group ($P = .233$). The incidence of major bleeding of 0.54% (95% CI 0.2-2.0) in the low-dose group was not significantly different from the 0.29% (95% CI 0.2-0.5) in the high-dose group ($P = .376$). The incidence of 90-day mortality of 0.33% (95% CI 0.2-0.7) in the low-dose group was not significantly different from the 0.21% (95% CI 0.1-0.4) in the high-dose group ($P = .190$).

Low-Dose Aspirin vs Warfarin

There was a higher risk of symptomatic PE in patients who received warfarin for chemoprophylaxis (1.24%, 95% CI 0.8-2.0) compared to low-dose aspirin (0.33%, 95% CI 0.1-0.8) ($P = .008$). There was also a higher risk of symptomatic DVT with warfarin (1.68%, 95% CI 1.1-2.8) compared to low-dose aspirin (0.52%, 95% CI 0.2-1.5) ($P = .035$). There was no significant difference between warfarin (0.46%, 95% CI 0.2-1.0) or low-dose aspirin (0.54%, 95% CI 0.2-2.0) regarding major bleeding ($P = .836$). Additionally, there was no difference between warfarin (0.42%, 95% CI 0.2-0.8) and low-dose aspirin (0.33%, 95% CI 0.2-0.7) with respect to 90-day mortality ($P = .410$).

Duration of Prophylaxis

After controlling for low-dose and high-dose aspirin, patients treated with aspirin for <4 weeks had a higher risk of major bleeding (1.59%, 95% CI 0.4-6.3) compared to patients treated for 4 weeks (0.15%, 95% CI 0.02-1.0; $P = .045$) (Table 2). However, major bleeding in patients treated with aspirin for >4 weeks (0.31%, 95% CI 0.2-0.6) was not distinguishable from patients treated for 4 weeks ($P = .474$).

Patients treated with aspirin for <4 weeks had a significantly higher 90-day mortality incidence (1.95%, 95% CI 0.7-5.3) compared to patients treated for 4 weeks (0.07%, 95% CI 0.02-0.2) ($P = .001$). Additionally, the 90-day mortality incidence in patients treated with aspirin for >4 weeks (0.20%, 95% CI 0.1-0.3) was not significantly distinguishable from patients treated for 4 weeks ($P = .08$).

Regarding incidence of symptomatic DVT, there was no difference between 4 weeks of aspirin (0.61%, 95% CI 0.2-1.9) and <4 weeks (2.62%, 95% CI 0.7-8.5) ($P = .091$), or 4 weeks and >4 weeks (0.66%, 95% CI 0.3-1.4) ($P = .913$). There was also no significant difference between 4 weeks (0.36%, 95% CI 0.1-1.0) and <4 weeks (1.37%, 95% CI 0.4-5.1) regarding symptomatic PE ($P = .116$) or 4 weeks and >4 weeks (0.49%, 95% CI 0.3-0.9) ($P = .626$).

Discussion

In 2007, the AAOS issued a new guideline accepting aspirin 325 mg BID as an adequate means of thromboprophylaxis after TJA for patients with standard risk of PE and major bleeding, standard risk of PE and elevated risk of major bleeding, and elevated risk of PE and major bleeding groups separately [11]. However, our systematic review demonstrates that a lower daily dose of aspirin (<162 mg/d) is not inferior to high-dose aspirin for symptomatic VTE prevention, 90-day mortality, or major bleeding after TJA. Therefore, this study strongly suggests that low-dose aspirin may be considered as a standard protocol and added to new guidelines for thromboprophylaxis in patients undergoing TJA.

Many studies provide evidence that aspirin is an acceptable means of VTE prophylaxis after TJA [3,4,6,7,20,22–24,60–63]. However, the appropriate dose of aspirin remains controversial. The studies included in this systematic review reported the various daily doses of aspirin of 75 mg/d [25,26], 81 mg/d [27], 100 mg/d [28–30], 150 mg/d [31], 160 mg/d [11,32], 300 mg/d [33], 325 mg/d [34–36], 650 mg/d [3,5–7,11,15,22–24,37–45], 1000 mg/d [46], 1200 mg/d [24,47–51], and 1300 mg/d [52–59]. Low-dose aspirin has been shown to be as effective as higher doses of aspirin in patients with acute coronary syndrome [64] and transient ischemic attack or minor stroke [65]. A systematic review and meta-analysis by Bundhun et al investigated the clinical outcomes after treatment of high-dose vs low-dose aspirin following percutaneous coronary intervention. The study found a higher association of major adverse cardiac events such as death, myocardial infarction (MI), and revascularization when high-dose aspirin was given compared to low-dose aspirin [66]. Additionally, Taylor et al [67] found a decreased risk of stroke, MI, and death within 30 days and 3 months after carotid endarterectomy when patients were treated with low doses of aspirin (81 or 325 mg/d) compared to higher doses (650 or 1300 mg/d).

Table 2
Effect of Duration of Aspirin Treatment on the Incidence of Symptomatic PE, DVT, 90-D Mortality, and Major Bleeding.

Outcome	< 4 Wk	4 Wk[a]	*P*-Value	> 4 Wk	*P*-Value
Symptomatic PE	1.37% (0.4-5.1)	0.36% (0.1-1.0)	.116	0.49% (0.3-0.9)	.626
Symptomatic DVT	2.62% (0.4-5.1)	0.61% (0.2-1.9)	.091	0.66% (0.3-1.4)	.913
90-D mortality	1.95% (0.7-5.3)	0.07% (0.02-0.2)	**.001**	0.2% (0.1-0.3)	.080
Major bleeding	1.59% (0.4-6.3)	0.15% (0.02-1.0)	**.045**	0.31% (0.2-0.6)	.474

Data are presented as percentage of outcome with 95% confidence intervals in parentheses. Bold *P*-values indicate a statistically significant value.
PE, pulmonary embolism; DVT, deep vein thrombosis.
[a] Comparison/reference group.

The pulmonary embolism prevention trial investigated low-dose aspirin (160 mg/d) vs placebo for 35 days in 13,356 patients undergoing surgery for hip fracture and 4088 patients undergoing elective arthroplasty from 1992 to 1998 [32]. This randomized trial found a 36% reduction in PE and symptomatic DVT and a 58% reduction in fatal PE when low-dose aspirin was used after hip fracture surgery as well as proportional effects after elective joint arthroplasty. Our data, as well as the results of the pulmonary embolism prevention trial [32] and other studies [11,12,68], suggest that low-dose aspirin provides adequate VTE prophylaxis after TJA.

Although many studies have demonstrated the benefits of aspirin, other studies suggest that aspirin may be less effective than other prophylactic drugs [37,50,69,70]. A meta-analysis by Imperiale and Speroff [69] found no significant difference in incidence of PE or DVT between aspirin and control groups after THA, while low-molecular-weight heparin (LMWH) with compression stockings was significantly more effective than the control. Additionally, a study by Jameson et al [71] looked at 108,584 patients undergoing either aspirin or LMWH treatment after THA and found that there was no significant difference between 90-day mortality in the 2 treatment groups, but slightly higher death was found in the aspirin group. A study by the National Joint Registry found that aspirin had an increased risk of returning to theater of postoperative wound complications 30 days after surgery compared to LMWH [72]. Kim et al evaluated low-molecular-weight dextran, aspirin, and control groups as thromboprophylactic agents after THA. Their data suggested that low-molecular-weight dextran provided better DVT thromboprophylaxis after THA compared to the control group and furthermore did not find a significant difference in incidence of DVT between the aspirin and the control group [50]. However, this study only investigated 150 patients and their reported values of DVT prevalence are high compared to our data. Additionally, our systematic review only included symptomatic VTE, while Kim et al [50] included asymptomatic VTE diagnosed by contrast venography.

It is well-established that long-term aspirin treatment is associated with GI bleeding and ulceration [73–75], but studies have found that the risk of gastrotoxicity is dose-related [75,76] and GI bleeding is more strongly related to the dose of aspirin than the duration of treatment [73]. Low doses of aspirin decrease the synthesis of the platelet aggregating agent thromboxane A2 [67] via irreversibly inhibiting cyclooxygenase-1 [77]. However, high doses of aspirin suppress prostacyclin metabolism [67] by irreversibly inhibiting cyclooxygenase-2, which is associated with inflammatory mediators [78]. Higher doses of aspirin may lead to the loss of the local defense mechanisms and cause increased ulceration and bleeding in the GI mucosa [76].

Although we expected a higher incidence of major bleeding associated with high-dose aspirin compared to low-dose aspirin, our data did not show any difference in major bleeding between the 2 doses. A prior study found that high-dose aspirin had significantly more Thrombolysis in Myocardial Infarction (TIMI) defined minor bleeding after percutaneous coronary intervention compared to low-dose aspirin [66]. Laine et al [79] did not find an increase in gastric ulceration when low-dose aspirin (81 mg/d) was used in osteoarthritic patients for 12 weeks. In this systematic review, we were not able to include minor bleeding or GI symptoms, which are significant side effects of aspirin that may play a role in determining the appropriate dose and duration of treatment. Although our data did not show an association between dose of aspirin and major bleeding, the lowest dose of aspirin to achieve maximum VTE protection should be used to avoid potential side effects.

The incidence of symptomatic PE for low-dose and high-dose aspirin in this study was 0.33% and 0.65%, respectively. The incidence of symptomatic DVT for low-dose and high-dose aspirin was 0.65% and 0.99%, respectively. There was no significant difference between the incidence of symptomatic DVT or PE regarding low-dose or high-dose aspirin. The low prevalence of symptomatic VTE while using aspirin was comparable to previous studies [11,20,80], further supporting the efficacy of aspirin after TJA.

The optimum duration for VTE prophylaxis remains controversial because the appropriate length of aspirin prophylaxis after TJA is not well studied. The studies included in this systematic review reported various durations of aspirin prophylaxis including 14 days [28,29,46,50], 21 days [52,58], 3 weeks [51], 1 month/4 weeks [11,34,35,37,40,44], 5 weeks [32], and 6 weeks [3,7,15,22,23,25,26,31,38,39,42,43,53,54]. We found no significant difference between incidence of PE or DVT and the different durations of aspirin treatment examined (<4 weeks, 4 weeks, and >4 weeks). Studies have shown that the risk for VTE after TJA can last for up to 1 month after TKA and 3 months for THA [81]. Additionally, studies have indicated that the coagulation cascade may remain activated for up to 5-6 weeks after proximal femur fracture [82]. However, a study by Parvizi et al [83] showed that the highest prevalence of symptomatic VTE occurs 1 week after TJA, with approximately 94% of all VTEs occurring within only 2 weeks after surgery. Although our study did not find an association between incidence of VTE and duration of aspirin treatment, it is important to continue prophylaxis as recommended in order to avoid this devastating complication.

There was a significantly higher incidence of 90-day mortality when patients were treated with aspirin for <4 weeks (1.95%) compared to those treated for 4 weeks (0.07%) or >4 weeks (0.20%). It is possible that the statistically significant increased risk of 90-day mortality associated with <4 weeks of prophylactic treatment may be due to arterial thrombosis or cardiac-related mortality [16], or premature cessation of therapy not documented in the examined studies. The most common cause of death after TJA is not VTE, but cardiovascular complications for both hip arthroplasty [84–86] and knee arthroplasty [86]. Blom et al [87] also found ischemic heart disease and cerebrovascular events contributing more to mortality after hip fracture than PE.

Aspirin has been shown to be a cardioprotective drug that can effectively prevent occlusive vascular events [88,89]. The Antithrombotic Trialist's Collaboration meta-analysis found a 12% reduction in serious vascular complications including MI, stroke, or vascular death when aspirin was used in primary prevention, in addition to a one-fifth reduction in non-fatal MI [90]. In secondary prevention, the Antithrombotic Trialist's collaboration found an even greater decrease in serious vascular events and also a significant reduction in total stroke and coronary events [90]. The ACCP recommends a low dose of aspirin (75-100 mg/d) for primary cardiovascular prevention for patients older than 50 years of age (Grade 2B evidence) and also recommend long-term low-dose aspirin for patients with established coronary artery disease (Grade 1A) [91]. In 2012, the ACCP recommended aspirin prophylaxis for 10-14 days after orthopedic surgery (Grade 1B), but also endorsed extending prophylaxis up to 35 days postoperatively (Grade 2B) [10]. However, the AAOS current guidelines recommend aspirin 325 mg BID for 6 weeks after orthopedic surgery [11]. Prior evidence supports the potential benefit of long-term cardioprotection from aspirin [89–91]. Parry et al [26] found a statistically significant decrease of 0.75% (13/1727) to 0% (0/1549) of cardiovascular deaths after 1727 patients were treated with low-dose aspirin (75 mg/d) for 6 weeks after elective THA compared to patients not treated with any chemoprophylaxis. Because there were increased deaths associated with a lower duration of aspirin (<4 weeks), the cardioprotective properties of aspirin may aid in decreasing mortality in patients treated for at least 4 weeks after surgery.

Because aspirin is an antithrombotic agent, we expected a higher incidence of major bleeding when patients were treated with aspirin for a greater duration. We expected that a longer exposure to aspirin would lead to a higher risk of major bleeding since aspirin can cause GI ulceration and bleeding [73–75]. However, our data suggest that patients had a higher prevalence of major bleeding when treated with aspirin for less than 4 weeks (1.59%) compared to 4 weeks (0.15%) or greater than 4 weeks (0.31%). Although this value was statistically significant, this trend may not be clinically relevant as the reporting of this side effect is often not uniform.

This systematic review found a higher risk of symptomatic PE and DVT when warfarin was used as the sole chemoprophylactic agent compared to low-dose aspirin, which is consistent with previous studies [3,14]. Although our study did not find a significant difference in major bleeding between aspirin and warfarin, prior studies have shown increased incidence of major bleeding in patients treated with warfarin compared to aspirin [6,15,17]. We were not able to collect and include data for wound complications as part of our analysis, but prior studies have shown higher wound complications in patients treated with warfarin compared to aspirin after TJA [9,17]. A disadvantage of warfarin is international normalized ratio testing and dose adjustments, which aspirin does not require. Additional laboratory testing, lower complication rates [9,17], and shorter length of hospitalization [3] suggest that aspirin is more cost-effective than warfarin [92,93]. Nam et al [17] found that patients treated with aspirin after THA also had a higher patient satisfaction at 2 weeks and 4-6 weeks postop compared to patients treated with warfarin. Our study further suggests the additional advantage of aspirin as a superior thromboprophylactic agent compared to warfarin.

We acknowledge certain limitations to this study. First, we did not exclude low levels of evidence, thus we were limited by the inclusion of low-quality studies in our analysis. Additional high-quality randomized controlled trials (RCT) are needed to further understand the effects of aspirin prophylaxis after TJA. However, the number of patients in an RCT required to reach adequate statistical power is very high due to the low incidence of symptomatic PE and DVT after TJA [11,20,80]. Also, because aspirin is considered an inexpensive drug compared to other anticoagulants, such RCTs may be precluded due to a lack of funding available. In some circumstances, it may be unethical to randomize these patients as the type of prophylaxis is often chosen based on patient history and comorbidities. In addition, allocation bias may be a concern when determining the type of treatment each patient should receive. Bozic et al [14] attempted to control for allocation bias, but found that patients treated with aspirin after TKA were significantly younger than patients treated with warfarin and also had lower baseline VTE risk score and shorter length of stay than warfarin or LMWH/fondaparinux patients. In addition to the type of prophylaxis, these data prompt further investigation into whether patient risk stratification may significantly influence the effectiveness of VTE prevention. A significant limitation in this study was the inability to assess for risk profile among the patients allocated to get low-dose vs high-dose aspirin. Future studies should determine any association with patient comorbidities and demographics to the efficacy of low-dose and high-dose aspirin.

Furthermore, we were not able to collect data regarding minor bleeding or blood transfusions of less than 2 units since these data were not consistently documented. If reported, we did consider 2 or more units of blood transfusion as suggestive of major bleeding. However, future studies should examine complications such as minor bleeding and the need for precise blood transfusions in patients receiving aspirin. The type of anesthesia, Charlson comorbidity index, and patient compliance were not collected in this systematic review. It is important to consider the impact of these factors in future studies to identify their possible association with efficacy of VTE prophylaxis. Additionally, we did not have the statistical power to compare other anticoagulants to low-dose aspirin besides warfarin. Future studies should investigate the benefit of low-dose aspirin compared to other anticoagulants after TJA. Another limitation to this analysis was that we did not control for the dose or duration of warfarin used. We did not find any difference between low-dose aspirin and warfarin regarding major bleeding or mortality. However, if we had differentiated high-dose warfarin to low-dose warfarin, we may have found a correlation between warfarin treatment and higher rates of major bleeding compared to aspirin. In addition, we compared warfarin to aspirin without knowing the therapeutic level of the drug, which is another limitation of this study.

In conclusion, aspirin is considered an acceptable means of thromboprophylaxis after TJA. This study suggests that low-dose aspirin is not inferior to high-dose aspirin for thromboprophylaxis in patients undergoing TJA. Additionally, patients treated with aspirin for less than 4 weeks may have a higher risk of major bleeding and 90-day mortality compared to patients treated for a longer duration. Although there was no significant benefit regarding the duration of aspirin on symptomatic VTE prevention, the decreased mortality and major bleeding in longer durations may support the continued recommendation of 6 weeks for prophylaxis after TJA. Our results support low-dose aspirin as an appropriate means of VTE prevention after TJA. Further prospective randomized controlled studies are needed to determine a potential advantage between daily vs twice daily aspirin dosage in order to fully understand the adequate dose and duration of aspirin thromboprophylaxis after TJA.

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