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REVIEW

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Low-versus high-dose aspirin for venous thromboembolic prophylaxis after total joint arthroplasty: a systematic review and meta-analysis

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Abstract

Background The adverse effects of aspirin are dose-dependent, and there is controversy surrounding the use of low-dose (LD) aspirin to prevent venous thromboembolism (VTE) following total joint arthroplasty (TJA). This meta-analysis sought to compare the efficacy and complication rate of low-dose (162 mg per day) versus high-dose (HD, 650 mg per day) aspirin after TJA surgery.

Methods In four main databases, we searched from inception until September 2024 for articles comparing the rate of VTE following TJA(TKA/THA) using only aspirin chemoprophylaxis with different dosages. We meta-analyzed and compared the VTE and complication rates of LD aspirin (162 mg per day) with HD aspirin (650 mg per day) and presented our results as odds ratio (ORs) in forest plot diagrams.

Results There were 14 eligible studies, comprising 43,518 patients in the LD group and 62,645 patients in the HD group. DVT (OR: 1.37, CI: 0.93–2.02, $P=0.11$) and PE (OR: 1.86, CI: 0.73–4.72, $P=0.19$) rates were similar between the groups. However, taking VTE as the total number of cases with DVT or PE, the incidence was significantly higher in the HD group than in the LD group (OR:1.53, CI: 1.17-2.00, $P=0.002$). HD also had a significantly higher rate of PJI (OR:2.68 CI:1.5–4.6 $P=0.001$), but gastrointestinal bleeding (GIB) was similar between the two groups (OR: 0.97, CI: 0.42–2.22, $P=0.95$).

Conclusion The findings suggest that LD aspirin may be a viable option for VTE chemoprophylaxis following TJA, potentially offering comparable efficacy with a lower risk of PJI compared to HD aspirin regimens.

Level of Evidence : Therapeutic Level II.

Keywords Arthroplasty, Aspirin, TKA, THA, PE, VTE, DVT

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Introduction

Venous thromboembolism (VTE) is a serious risk for all patients undergoing TJA due to the long duration of the surgery and reduced mobility postoperatively [1–4]. Considering that VTE is a major cause of morbidity, mortality, and health care costs, accurate prevention protocols are necessary [5]. Hospital-acquired deep vein thrombosis (DVT) following arthroplasty without prophylaxis is approximately 40–60% [6], and the incidence of DVT increases mortality risk by 7% when compared to patients without VTE [7]. There is a concern even for anticoagulated patients with DVT rates up to 5% and pulmonary thromboembolism (PE) rates up to 2% [8]. Therefore, Prophylaxis against VTE after TJA is essential [9].

The benefits of aspirin as a prophylactic agent include safety, lower incidence of hematomas and other complications, affordability, no monitoring requirement, and good tolerance. This suggests that aspirin may be an appropriate option [10–14]. A substantial body of evidence suggests the effectiveness of aspirin in preventing postoperative VTE [5, 8, 15–18]. In recent decades, PE rates following TJA have not reduced significantly [19]; and studies have shown that potent anticoagulants (e.g. LMWH and NOACs) contribute only to a reduction in asymptomatic VTE [20–22]. Potent anticoagulants have been proposed to reduce major complications, but their effectiveness has been questioned as PE continues to happen [23–25]. Compared to simple aspirin, they may increase wound complications, bleeding, and hospitalization days [26–28]. However, despite decades of successful and safe use, aspirin use as a sole prophylactic antithrombotic agent remains controversial. In most studies, healthy and normal-risk patients were included, so the controversy is more prominent among other groups [29].

Both the American Association of Orthopedic Surgeons (AAOS 2009) and the American College of Chest Physicians (ACCP 2012) recommended that aspirin can be used as the only chemoprophylactic agent after TJA. The recommended dose was 325 milligrams twice daily for six weeks following surgery [30, 31]. Meanwhile, LD aspirin was voted as the most effective and safest chemoprophylaxis by 77% of attendees at the International Consensus Meeting (ICM) 2022 [32]. Since gastrointestinal adverse effects are dose-dependent, and there is conflicting evidence supporting the use of LD aspirin for preventing VTE after TJA, the optimal dose of aspirin for VTE prevention after TJA was unclear until recently [33].

To this end, this meta-analysis on comparative studies aimed to compare symptomatic VTE rates following TJA with chemoprophylaxis of LD aspirin (162 mg per day) versus HD aspirin (650 mg per day). Our secondary objective was to examine differences in adverse event rates, including gastrointestinal bleeding (GIB) events and periprosthetic infection (PJI).

Materials and methods

This systematic review and meta-analysis study was conducted according to the Cochrane Collaboration & preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. This study was registered with PROSPERO (International Prospective Register of Systematic Reviews, registration ID: CRD42022342101).

PECOT; Patients (P), Exposure (E), Comparison (C), Outcome (O), and Type (T)

The present study examined the VTE rate (O) in patients undergoing TJA (P) when treated with LD aspirin (162 mg per day) (E) as opposed to HD aspirin (650 mg per day) (C) and only included comparative cohort studies consisting of 2 ≤ groups of doses (T).

Search strategy and screening

Four electronic databases (Scopus, PubMed, Web of Science, and Embase) were searched thoroughly from inception until September 2024. A hand search was conducted in addition to the electronic searches. Several keywords and Medical SubHeadings (MESH) terms were used in our search strategy for "Total joint arthroplasty", "aspirin", and "Dosing" and modified according to the search rules of each database (Supplementary Material No. 1). All records were imported using the Covidence online systematic review software (https://www.covidence.org). Following the elimination of duplicate studies, the record was independently reviewed by two reviewers (P.R. and F.P.) applying a distinct inclusion/exclusion criterion. A third reviewer (P.M.) was consulted in cases of conflict.

Inclusion and exclusion criteria

Inclusion: [1] TJA (TKA or THA) both primary or revision surgery [2], Mean follow-up period of at least 1 month [3], Having at least two groups with the VTE chemoprophylaxis of LD and HD aspirin [4], Reporting at least one primary or secondary outcome of interest (VTE, DVT, PE).

Exclusion: [1] Reviews, technique articles, case reports, conference abstracts, and expert-opinion studies [2] Using other anticoagulant medications such as warfarin or NOAC or LMWH [3], Studies with no control groups [4], non-English studies [5] Patients with coagulopathies.

Data extraction and synthesis

The full text of eligible studies was reviewed in depth, and the data were extracted using a pre-designed Excel spreadsheet: General information and demographics, primary outcome (symptomatic DVT, symptomatic PE, and symptomatic VTE (DVT or PE), and secondary (GIB, Total GI complications (Bleeding + Ulcer), PJI, and other complications).

Quality assessment and level of evidence

Newcastle-Ottawa Scale (NOS) [34] was used to assess the quality of observational studies (retrospective or prospective cohorts). This tool contains eight items classified into three categories: selection, comparability of study groups, and assessment of results. An overall score can range from 0 to 9; a score of seven or more points indicates high quality, while a score of less than four points indicates low quality. We wrote levels of evidence in the same manner as they were described in the original study. Studies without evidence levels were identified using the Guidelines for Evidence-Based Medicine (CEBM) [35].

Statistical analysis

Comprehensive meta-analysis software (version 3) was employed for the meta-analysis of the relevant outcome measures. The pooled rate of the primary outcomes (VTE, DVT, and PE) and secondary outcomes (GIB, PJI, etc.) after TJA was compared between the LD and HD aspirin groups and presented as odds ratios (ORs). Publication bias was assessed using a funnel plot and Egger's test. I^2 tests were used to identify heterogeneity in the studies included, and random effects models were used when $I^2 > 30\%$ [36]. To identify heterogeneity sources, sensitivity analysis was used. Statistical significance was determined by the P-value of < 0.05.

Results

Study selection

The search strategy revealed 1177 results. After duplicate results were excluded, 579 results remained for screening. Title/abstract screening excluded 562 studies, leaving 17 studies for full-text screening. Two studies were also included by citation searching. after full-text screening, 14 studies were found to be eligible to be included in the study [33, 37–49] (Fig. 1).

Study characteristics [Table 1]

Included studies were all observational cohort studies published from 2017 until 2023; three of them were prospective cohorts [38, 42, 49] and eleven were retrospective cohorts [33, 37, 39–41, 43–48]. Thirteen studies were conducted in the USA [33, 37–48] and one was conducted in Iran [49]. Except for one study, all studies consist of two groups: 162 mg per day (81 mg twice daily) and 650 mg per day (325 mg twice daily) aspirin [Table 1]. The groups included in Watts et al. study included 81, 162, 325, and 650 mg of aspirin per day. Thus, we compared the 162 mg dosage of aspirin to the 650 mg dosage to obtain more valid results.

The eligible studies included a total of 106,163 patients of which 41% (43,518) were in the LD (162 mg) group and 59% (62,645) were in the HD group (650 mg). All the studies prescribed aspirin (162 mg or 650 mg) for 4–6 weeks as chemoprophylaxis; Except for Najafi et al.

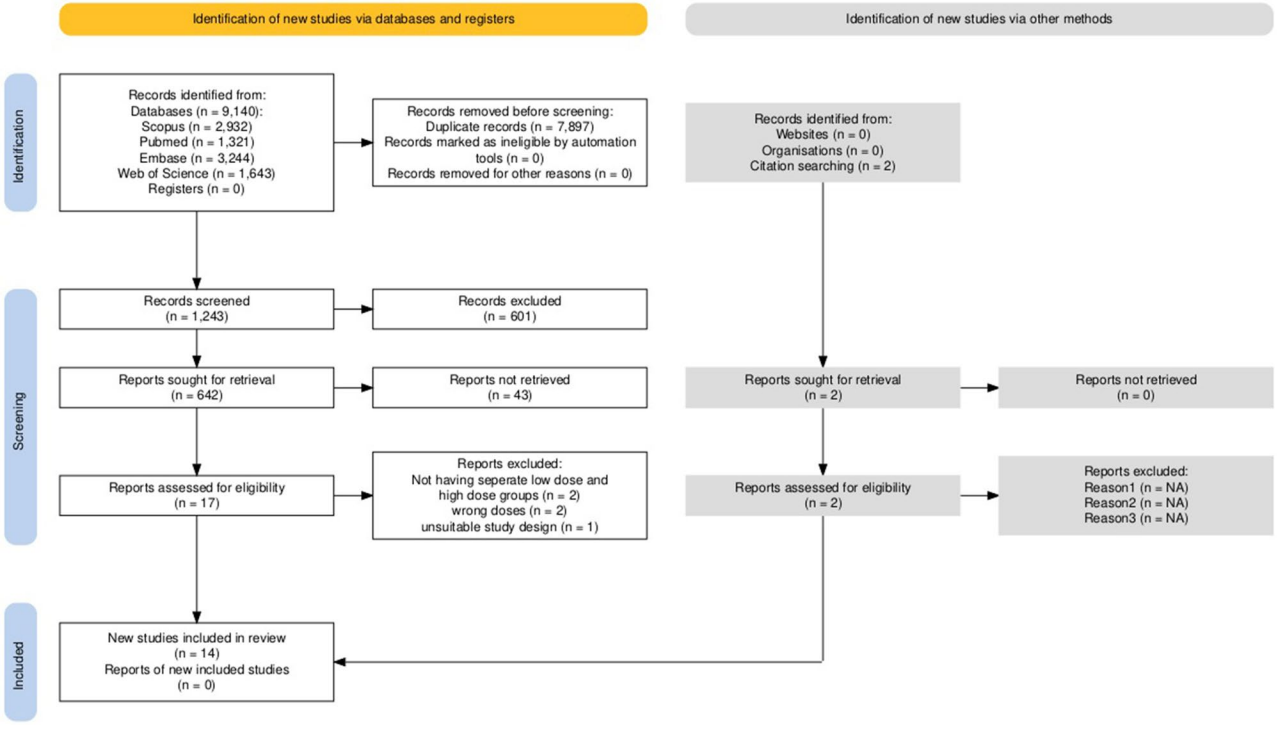

Fig. 1 Prisma diagram of the study selection

Table 1 Summary of study characteristics

No.	Study	Surgery Type	Cohort Groups	Age (mean ± SD)	Follow-up	Intervention protocol	Outcome measure(s) (primary/secondary)
1	Shafiei 2023	Primary or revision TJA	Total = 312 Low-dose = 158 High-dose = 154	54.2 ± 18.6 53.3 ± 18.4 55.0 ± 18.9	90 days	6 weeks of 81 mg/325 mg BD post-operatively	Primary: DVT PE Secondary: GIB Death
2	Merkow 2021	Primary TKA	Total = 12,866 Low-dose = 3453 High-dose = 9413	N/A	90 days	4–6 weeks of 81 mg/325 mg BD post-operatively	Primary: DVT PE
3	Uvodich 2021	Primary TJA	Total = 3512 Low-dose = 961 High-dose = 2551	66 ± N/A 67 ± N/A 66 ± N/A	90 days	4–6 weeks of 81 mg/325 mg BD post-operatively	Primary: DVT PE Secondary: GIB
4	Faour 2019	Primary THA	Total = 3936 Low-dose = 1033 High-dose = 2903	64.5 ± 12 66 ± 12 64 ± 12	90 days	4–6 weeks of 81 mg/325 mg BD post-operatively	Primary: DVT PE Secondary: GIB Death
5	Najafi 2022	Primary THA and TKA	Total = 15,825 Low-dose = 8761 High-dose = 7064	N/A	30 days	At least 2 weeks of 81 mg/325 mg BD post-operatively	Primary: PJI Secondary: GIB
6	Shohat 2021	Primary TKA	Total = 9208 Low-dose = 4413 High-dose = 4795	65.5 ± 9.0 65.5 ± 8.7 65.4 ± 9.3	30 days	4 weeks of 81 mg/325 mg BD post-operatively	Primary: DVT PE Secondary: MBE
7	Hood 2020	Primary THA and TKA	Total = 404 Low-dose = 205 High-dose = 199	N/A	30 days	4 weeks of 81 mg/325 mg BD post-operatively	Primary: Patient Compliance Secondary: GI complications
8	Feldstein 2017	Primary THA and TKA	Total = 643 Low-dose = 361 High-dose = 282	63.8 ± 9.7 64.0 ± 10.0 63.5 ± 9.4	30 days	4 weeks of 81 mg/325 mg BD post-operatively	Primary: DVT PE Secondary: Bleeding, Rash, Infection
s	Parvizi 2017	Primary TJA	Total = 4651 Low-dose = 1459 High-dose = 3192	64.0 ± 10.7 63.7 ± 11.7 64.7 ± 10.2	30 days	4 weeks of 81 mg/325 mg BD post-operatively	Primary: DVT PE Secondary: GIB Death
10	Tang 2020	revision THA	Total = 1361 Low-dose = 388 High-dose = 973	65.3 ± 12.1 66.2 ± 11.5 63.1 ± 12.4	90 days	4 weeks of 81 mg/325 mg BD post-operatively	Primary: DVT PE Secondary: GIB Death PJI
11	Faour 2018	primary TKA	Total = 5666 Low-dose = 1327 High-dose = 4339	68 ± 10 68 ± 10 68 ± 10	90 days	4 weeks of 81 mg/325 mg BD post-operatively	Primary: DVT PE Secondary: GIB Death
12	Tang 2021	Revision TKA	Total = 1438 Low-dose = 435 High-dose = 1003	63.4 ± 10.3 63.8 ± 9.3 63.2 ± 10.7	90 days	4 weeks of 81 mg/325 mg BD post-operatively	Primary: DVT PE Secondary: GIB Death PJI
13	Watts 2021	Primary and Revision TKA & THA	Total = 53,848 Low-dose = 19,341 High-dose = 25,329	6657 ± 10.09 66.5 ± 10.01 65.9 ± 10.04	40 days	4 weeks of 81 mg/325 mg BD post-operatively	Primary: Bleeding, MBE Secondary: VTE
14	Van Nest 2021	TKA and THA	Total = 1671 Low-dose = 1223 High-dose = 448	N/A	90 days	4 weeks of 81 mg/325 mg BD post-operatively	Primary: Heterotopic ossification

which reported at least two weeks of prescription following surgery.

After Arthroplasty, five studies followed the patients for 3 months [33, 39, 40, 43, 49]; 5 studies followed the patients for 1 month [37, 38, 42, 44, 47], and in one study, the patients were followed up for 40 days for any possible adverse effect [46].

Seven studies investigated the differences between the two dosing regiments after TKA [33, 38, 39, 43–45, 48]; five after THA [33, 38, 40, 41, 45]; and four studies did that for TJA without categorizing the results regarding THA and TKA cases [37, 42, 46, 47, 49].

Twelve studies assessed DVT, PE, and VTE in patients [33, 37–44, 46–49], eight studies investigated GIB [33, 37, 38, 40, 41, 43, 47, 48] and four studies evaluated total bleeding event without separating GIB from surgical site wound bleedings [39, 42, 44, 46]. Five studies assessed PJI [37, 38, 41, 47, 48]. Van Nest et al. also

studied heterotopic ossifications (HO) after arthroplasty [45]. A summary of Study Characteristics is presented in [Table 1].

Baseline characteristics of LD and HD groups

The LD and HD ASA groups were similar in regards to their sex (10 studies [16, 33, 41, 42, 44, 47, 50–53]), age (6 studies [16, 44, 47, 50, 52, 53]), BMI (7 studies [33, 40, 41, 47, 50–52]), Smoke (2 studies [41, 50]), co-morbidities (5 studies [16, 44, 47, 50, 51]), knee or hip arthroplasty (3 studies [42, 50, 53]), race (2 studies [44, 52]), and revision or primary surgery [50], general or spinal anesthesia [50], Length of stay [50], Operative time [41], tourniquet use [44], ASA score [44] (one study). Also, two studies did not report the baseline characteristics of groups [43, 45], and one study used a statistical model that controlled for confounders [46].

On the other hand, some baseline characteristics were different among groups in some studies. LD group patients were slightly older in four studies [33, 40–42], and vice versa in a single study [51]. Charlson Comorbidity Index (CCI) was lower in the LD group in one study [40] and vice versa in another single study [33]. LD group was associated with higher use of TXA [44, 47], spinal anesthesia [44, 47], and less tourniquet use [47, 52] ($n=2$ studies). Also, the LD group was associated with a higher rate of female patients [40], hip arthroplasty [47], diabetic mellitus [47], Lower ASA score [41], lower rate of bilateral surgery [47], lower blood transfusion rate [47], shorter length of stay [44], longer operative time [52], and different race [41] (all only in one study).

Quality assessment

Based on the Newcastle-Ottawa Quality Assessment Form for Cohort Studies (NOS), none of the studies were of low quality; 6 (43%) had fair quality and 8 (57%) studies had good quality [Table 2]. As for the level of evidence, two (14%) were level II, and twelve (86%) were level III.

Primary and secondary outcomes results

Primary outcomes

All studies except Van Nest et al. and Najafi et al. ($n=12$) reported at least one of the adverse effects of DVT, PE, and VTE as their primary outcome.

Symptomatic DVT Most of them found out that LD aspirin chemoprophylaxis is similar to the HD regiment regarding efficacy for DVT prophylaxis [33, 37, 38, 40, 41, 43, 44, 48, 49]. Moreover, Faour et al. revealed HD aspirin prophylaxis is significantly more likely to Symptomatic DVT (OR: 4.72, CI: 1.71–12.99, $P=0.00$) [39]. After conducting a meta-analysis, DVT rates were similar between groups (OR: 1.37, CI: 0.93–2.02, $P=0.11$); the results were the same in the subgroups analysis for TKA (OR:1.37, CI: 0.87–2.17, $P=0.17$) and THA (OR: 1.40, CI: 0.65–3.01, $P=0.39$) (Fig. 2). There was little heterogeneity in the analysis ($I^2=3.1\%$) and no publication bias was evident (Egger's test $P=0.33$) (Fig. 3).

Symptomatic PE Six studies reported no significant difference in PE occurrence between LD and HD regiments [38–41, 44, 48]. Merkow et al. revealed that LD aspirin is even superior in preventing PE (OR: 0.094, CI: 0.03–0.25, $P=0.00$) [43]. Meta-analysis of data from seven studies showed no significant difference between the LD and HD groups (OR: 1.86, CI: 0.73–4.72, $P=0.19$). The subgroup analysis also yielded similar results; There was no significant difference between the incidence of PE in both TKA (OR: 1.50, CI:0.41–5.50, $P=0.54$) and THA surgeries (OR: 2.33, CI:0.61–8.92, $P=0.22$) (Fig. 4). There was little heterogeneity in the analysis ($I^2=24.8\%$) and no publication bias was evident (Egger's test $P=0.54$).

Table 2 Quality Assessment by NOS and level of evidence

No.	First Author	Type of Study	Level of Evidence	Selection	Comparability	Outcome/Exposure	Overall Quality
1	Feldstein 2017	Retrospective Cohort	III	**	*	***	**Fair**
2	Parvizi 2017	Prospective Cohort	II	***	*	***	**High**
3	Faour 2018	Retrospective Cohort	III	****	**	***	**High**
4	Faour 2019	Retrospective Cohort	III	***	*	***	**High**
5	Hood 2020	Prospective Cohort	II	***	*	**	**High**
6	Tang 2020	Retrospective Cohort	III	****	**	***	**High**
7	Merkow 2021	Retrospective Cohort	III	***	*	***	**High**
8	Uvodich 2021	Retrospective Cohort	III	****	*	***	**High**
9	Shohat 2021	Retrospective Cohort	III	**	**	***	**Fair**
10	Tang 2021	Retrospective Cohort	III	****	*	***	**High**
11	Watts 2021	Retrospective Cohort	III	**	*	**	**Fair**
12	Van Nest 2021	Retrospective Cohort	III	**	**	***	**Fair**
13	Shafiei 2023	Prospective Cohort	III	**	*	***	**Fair**
14	Najafi 2022	Retrospective Cohort	III	**	*	***	**Fair**

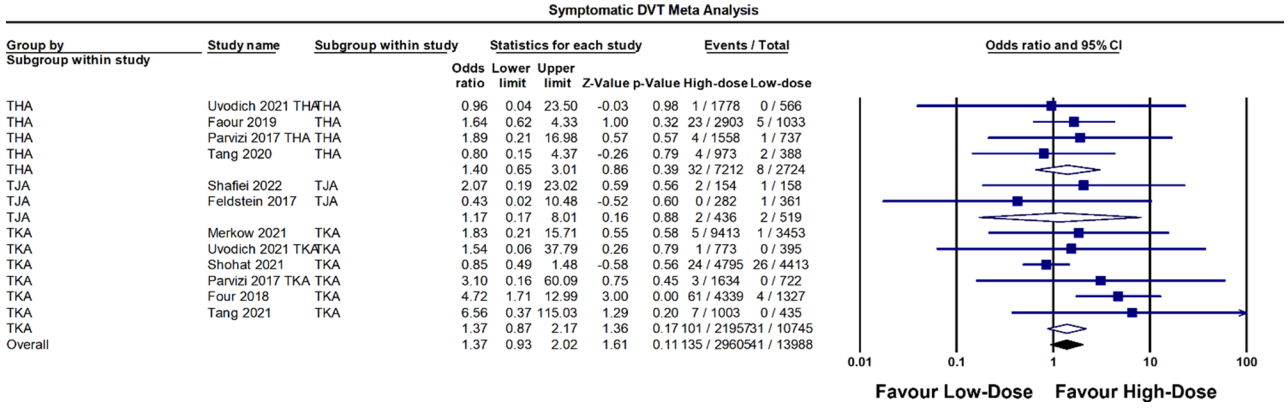

Fig. 2 Forest plot of DVT Meta-analysis showed no difference between the groups

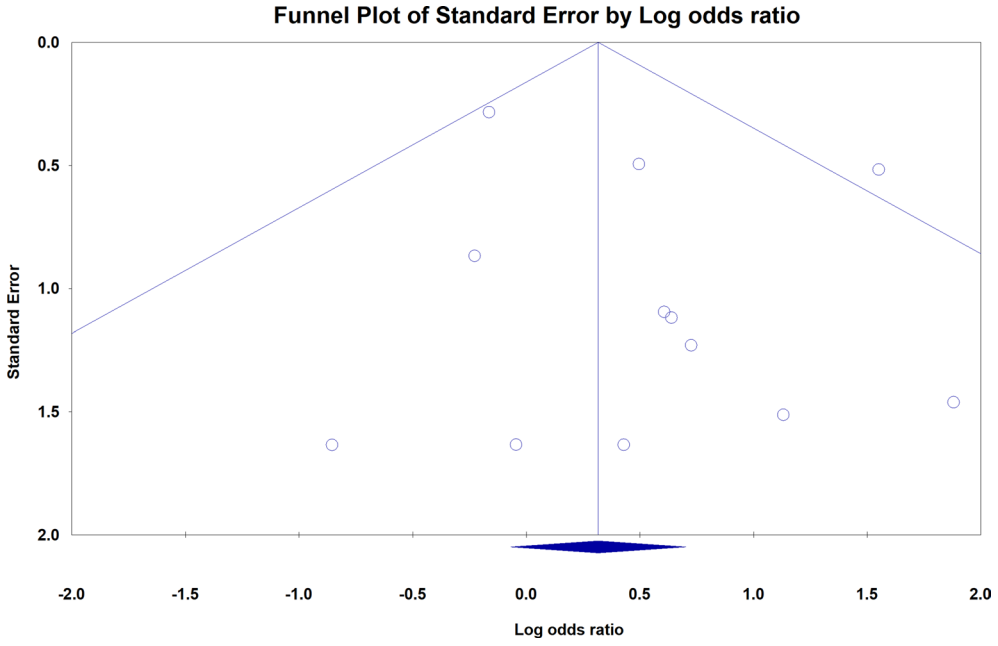

Fig. 3 Publication bias for DVT meta-analysis

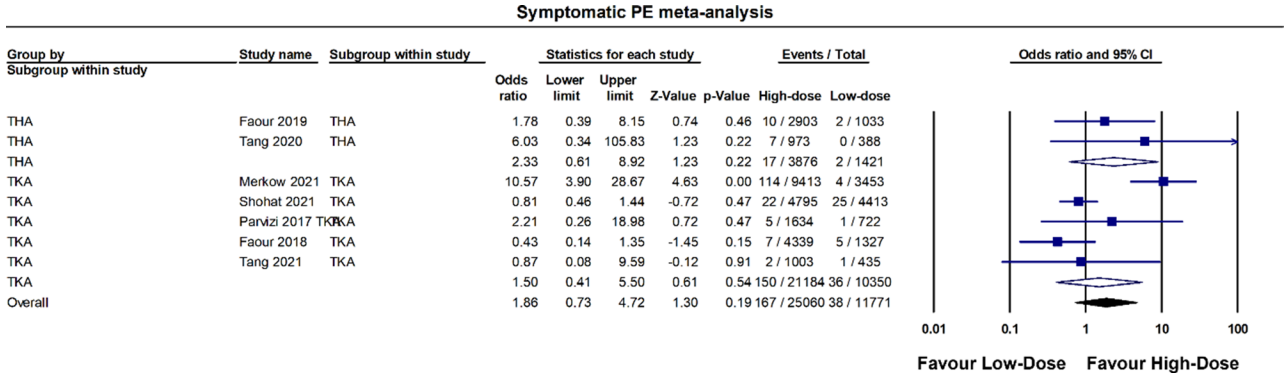

Fig. 4 Forest plot of the PE Meta-analysis showed no difference between the groups

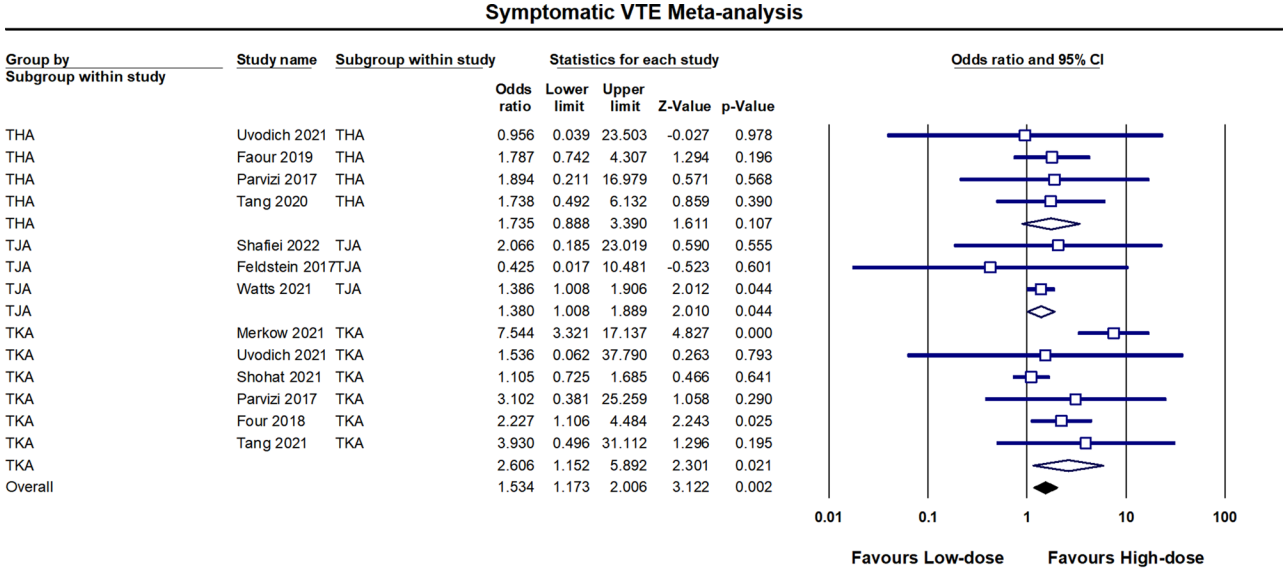

Fig. 5 Forest plot of VTE Meta-analysis showed a significantly lower rate for the LD Aspirin group

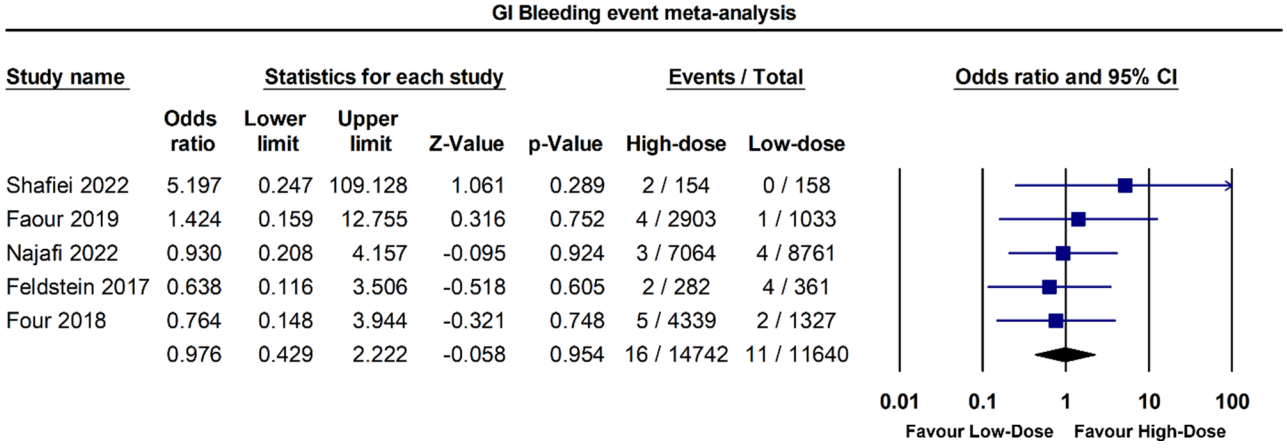

Fig. 6 Forest plot of GIB, Meta-analysis showed no difference between the groups

Symptomatic VTE VTE was considered the total number of cases who had DVT or PE. Eight studies reported VTE as a total number of DVT or PE cases to be not significantly different between LD and HD regiments [33, 37–41, 44, 48, 49]. Merkow et al., and Faour et al. reported the total number of VTE occurrences to be significantly higher in the HD regimen than in LD (OR: 7.54, $P=0.04$, and OR=2.23, $P=0.025$ respectively) [43, 46]. Meta-analysis showed that the incidence of VTE after arthroplasty was significantly higher in the HD group compared to the LD group (OR:1.53, CI: 1.17-2.00, $P=0.002$). The subgroup analysis showed that the incidence of VTE was higher significantly in the HD group in the TKA subgroup (OR: 2.60 CI:1.15–5.89, $P=0.021$). Unlike TKA, the difference between the two groups was not significant in THA (OR: 1.74 CI:0.89–3.39 $P=0.39$) (Fig. 5). There was medium heterogeneity in the analysis ($I^2=40.9\%$) and no publication bias was evident (Egger's test $P=0.32$); Influence analysis also showed that omitting each one the studies did not change the results significantly.

Secondary outcomes

Bleeding and ulceration The studies reported bleeding events in various ways. Some reported only GI bleedings (GIB) while some others reported GI bleedings and ulcerations together as GI complications. Also, some studies reported major bleeding events (MBE) as GIB and ulcerations, and surgical wound bleedings altogether.

Five studies reported GIB and all revealed that there is no significant difference between the two groups regarding GIB [37, 39, 40, 47, 49]. Meta-analysis also showed no significant difference between the two groups (OR: 0.97, CI: 0.42–2.22, $P=0.95$) (Fig. 6).

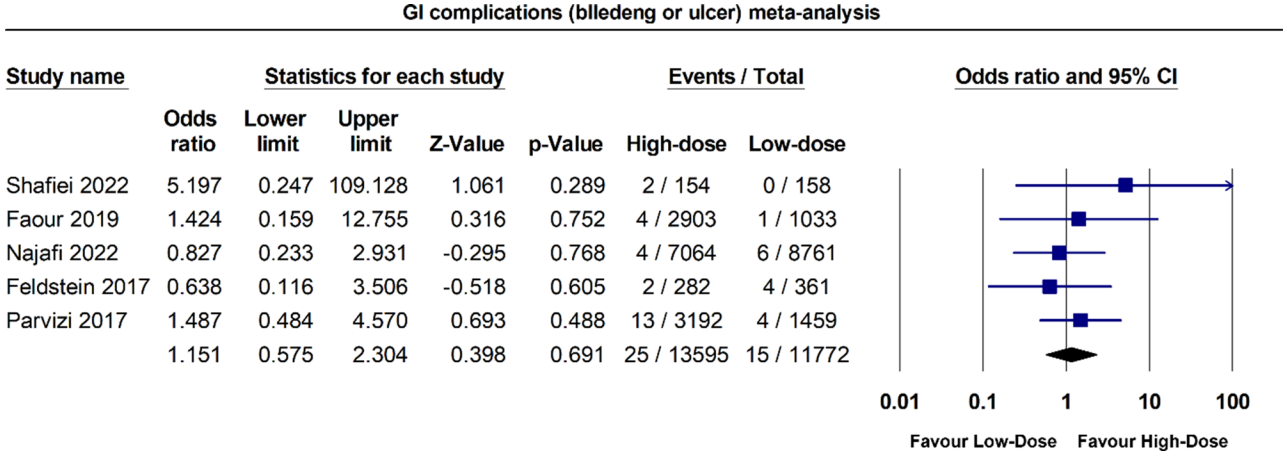

Fig. 7 Forest plot of GI complications, Meta-analysis showed no difference between the groups

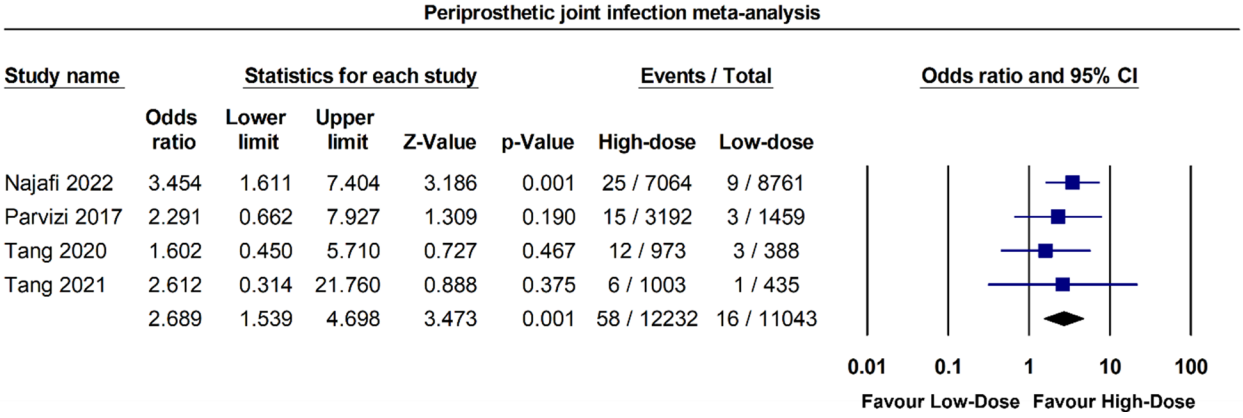

Fig. 8 Forest plot of PJI Meta-analysis showed a significantly lower rate for the LD Aspirin group

Five studies reported total GI complications and none of them found any significant difference between the two groups [37, 39, 40, 47, 49]. meta-analysis results showed no significant difference between the two groups (OR:1.15, CI:0.57–2.30, $P=0.69$) (Fig. 7).

Bleeding events (GI or wound) Three studies reported bleeding events, of which two found no significant difference between the two groups [39, 46]. Shohat et al. reported that the number of bleeding events was significantly higher in the HD group (OR:2.23 CI: 1.1–4.3 $P=0.02$) [44].

PJI: Three Studies measured the incidence of Periprosthetic Joint infections (PJI), two of which found no significant difference between the two groups [37, 38]. On the other hand, Najafi et al. found that in patients receiving HD prophylaxis the odds of PJI are significantly higher (OR:3.45 CI:1.6–7.4 $P=0.001$) [47]. Two studies also investigated deep wound infections and concluded that there was no significant difference between the LD and HD regimens [41, 48]. Meta-analysis showed that the HD group had a significantly higher rate of PJI (OR:2.68 CI:1.5–4.6 $P=0.001$) ($I^2=0$) (Fig. 8).

Sensitivity analysis performed for all the above analyses did not reveal any changes in the results when each study was left out. Due to the insufficient number of studies, it was not possible to conduct subgroup analysis in the case of secondary outcomes (GI bleeding, GI complications, and PJI). A summary of adverse effects separated based on the surgery type can be seen in Tables 3A, 3B, and 3C.

Other outcomes

Van Nest et al. studied the incidence of HO after TKA and THA. The rate of HO was higher in the HD group but the difference in both TKA or THA was not significant (OR:1.22 and 1.25, $P=0.38$ and 0.16, respectively) [45].

Four Studies reported death after arthroplasty. None of the studies found any significant correlation between the aspirin dose prescribed and the incidence of death (OR: 1.35, CI:0.441–4.129, $P=0.60$) [38–41].

Hood et al. also investigated patient compliance in the LD and HD regiments; their study showed that there was

Table 3 A. a summary of adverse events in all arthroplasty surgeries included

Adverse event	No. Studies	Low dose	High dose	Odds Ratio (95% CI)	*P*-value
Symptomatic DVT	10	0.45% (135/29605)	0.29% (41/13988)	1.37(0.93–2.02)	0.11
Symptomatic PE	7	0.32% (38/11771)	0.66% (167/25060)	1.86(0.73–4.72)	0.19
Symptomatic VTE	11	0.38% (128/33329)	0.74% (409/54934)	1.595(1.290–1.974)	0.000
GI Bleeding	5	0.09% (11/11640)	0.10% (16/14742)	0.976(0.429–2.222)	0.954
GI complications (bleeding or ulcer)	5	0.12% (15/11772)	0.18% (25/13595)	1.151(0.575–2.304)	0.691
Bleeding event (GI or Wound)	4	0.66% (167/25280)	0.79% (275/34668)	1.280(1.054–1.554)	0.020
PJI	4	0.14% (16/11043)	0.47% (58/12232)	2.689(1.539–4.698)	0.001

Table 3 B. a summary of adverse events in knee arthroplasty surgeries included

Adverse event	No. Studies	Low dose	High dose	Odds Ratio (95% CI)	*P*-value
Symptomatic DVT	6	0.28% (31/10745)	0.45% (101/21957)	1.37 (0.87–2.17)	0.17
Symptomatic PE	5	0.34% (36/10350)	0.70% (150/21184)	1.50(0.41–5.50)	0.54
Symptomatic VTE	6	0.53% (57/10745)	1.14% (252/21957)	1.821(1.321–2.510)	0.000

Table 3 C. a summary of adverse events in hip arthroplasty surgeries included

Adverse event	No. Studies	Low dose	High dose	Odds Ratio (95% CI)	*P*-value
Symptomatic DVT	4	0.29% (8/2724)	0.44% (32/7212)	1.40(0.65–3.01)	0.39
Symptomatic PE	2	0.14% (2/1421)	0.71% (7/973)	2.33(0.61–8.92)	0.22
Symptomatic VTE	4	0.36% (10/2724)	0.25% (4/1558)	1.735(0.492–6.132)	0.107

no significant difference between different age or dosing groups, sex, or the procedure done (TKA or THA) in patient compliance with medication use [42].

Discussion

This meta-analysis revealed that there was no statistically significant difference in thromboembolism events (DVT, PE) or GIB between the HD aspirin (650 mg daily) group and the LD aspirin (162 mg daily) group. However, the incidence of total VTEs was significantly higher in the HD group compared to the LD group (OR=1.53, *P*=0.002), particularly in the TKA subgroup. Moreover, compared to the LD group, the HD group showed a much greater rate of PJI (OR=2.69, *P*=0.001). Both groups experienced similar levels of GIB and other complications. Sensitivity analysis did not alter the findings, indicating the robustness of the results. These findings suggest that LD aspirin may be a viable option for VTE chemoprophylaxis following TJA, potentially offering comparable efficacy with a lower risk of adverse events compared to HD aspirin regimens. When interpreting the results, it's important to note that the LD group was slightly older and exhibited some distinct characteristics compared to the HD group in some studies. For example, the distribution of comorbidities was inconsistent.

Patients undergoing arthroplasty are at higher risk of developing VTE and subsequent PE due to surgery procedures and immobility, which can be fatal [10, 54–56]. In ACCP guidelines from 2012, aspirin was recommended as an appropriate method of VTE prophylaxis after TJA [30]. To choose the most effective chemoprophylactic agent and dosage profiles, it is essential to weigh the benefits of agents against the adverse effects of drugs with higher risk profiles [12]. The mechanism of action of aspirin differs significantly from that of traditional anticoagulants. While anticoagulants target the coagulation cascade to prevent thrombus formation, aspirin primarily inhibits platelet aggregation through irreversible COX-1 inhibition. This distinction may partially explain the comparable efficacy of LD aspirin to HD aspirin, as higher doses may impair platelet and coagulation function excessively. Moreover, postoperative mobilization is a critical component in VTE prophylaxis and might have confounded the results of included studies. Variability in mobilization protocols and adherence could influence VTE incidence independently of aspirin dosage. Finally, the higher risk of complications in the HD group could reflect differences in patient characteristics, as older patients, or those with significant comorbidities, such as obesity or a history of VTE, are often prescribed higher aspirin doses. These factors warrant further investigation to clarify their interaction with aspirin dosing regimens. Numerous meta-analyses have been done showing that aspirin is not inferior to anticoagulants, if not superior [5, 57–69]. While LD aspirin carries a lower risk of GIB and PJI, it has similar benefits in preventing VTE incidents following arthroplasty surgery compared with other chemoprophylactic agents, such as LMWH [70–76]. However, recent literature disproves the claim that HD aspirin (650 mg daily) provides more protection against thromboembolism accidents than LD aspirin (150–200 mg daily) [77–79]. In the Pulmonary Embolism Prevention (PEP) study in 2001, LD aspirin (160 mg daily) significantly lowered the incidence of DVT and PE in patients

undergoing TJA by at least one-third of place controls [39]. Nonetheless, the AAOS 2011 guidelines recommend that HD aspirin (650 mg daily) be used to prevent VTE following TJA [80]. A similar systematic review conducted by Azboy et al. corroborated our findings in VTE. They found the incidence of symptomatic VTE incidents in the LD group was not significantly different from the HD group [81].

The possible higher incidence of VTEs following TJA in the HD group could potentially be attributed to a variety of factors. At lower dosages, aspirin functions nearly selectively and irreversibly inhibit cyclooxygenase-1 (COX-1), which leads to decreased synthesis of the platelet aggregation agent thromboxane A2. As the concentration of aspirin increases, the enzyme cyclooxygenase-2 (COX-2) is irreversibly inhibited and the synthesis of prostacyclin, which is associated with inflammatory mediators, is inhibited [81, 82]. Higher aspirin dosages may result in more potent and prolonged platelet inhibition compared to lower doses of aspirin [83, 84]. While platelet inhibition plays an essential role in preventing clot formation in blood vessels, higher aspirin doses may impair the hemostatic response to venous thrombosis, indicating an alteration in thrombotic pathways that contribute to the development of venous thromboembolism [85]. Aspirin's dosing regimen may influence its pharmacokinetics and pharmacodynamics [86]. HD aspirin regimens may cause greater fluctuations in plasma concentration levels, thus compromising antithrombotic efficacy and increasing the risk of VTE [87]. Aspirin undergoes first-order elimination, meaning the elimination pathways can get saturated with the higher doses of drug in the body. It is important to note that lower doses of aspirin are normally excreted through hepatic pathways; by conjugating with glycine and glucuronidation, glucuronide esters are produced and excreted. But in the higher doses, aspirin excretion becomes more reliant on renal pathways. Due to these facts, the half-life of aspirin varies between the 81 mg and 325 mg doses; with lower doses, the half-life is estimated to be 2–3 h, while in higher doses, it is estimated to be 15–30 h. this makes the time required for the drug to be considered completely out of the body to be 10–15 h for LD aspirin and 75–150 h for HD aspirin [88, 89]. This necessitates the careful monitoring of patients receiving aspirin as it does not have any known antagonist in case the patient suffers GIB or other acute toxicities or is required to undergo another operation, for example, revision surgery. There are, though, some strategies to prevent some side effects related to aspirin, for example, prescribing proton pump inhibitors (PPIs).

Postoperative management includes various factors that might influence the results of studies and introduce heterogeneity in the results. These include the routine thromboprophylaxis protocols employed in every institution; these protocols and the level of adherence in every institution can influence the complication rates to a high extent. Routine thrombosis prophylaxis strategies are typically consisted of a pharmacological and a mechanical part. The pharmacological part, which was the subject of our study, might utilize various drugs each with their own pros and cons. These include heparin (UFH or LMWH), aspirin, or direct oral anticoagulants (DOACs). On the other hand, confounder factors may play a role. Patients receiving HD aspirin after TJA might have different underlying risk factors for VTE than those using LD aspirin. Patients with comorbidities such as obesity, older age, and a history of previous VTE incidents may be more likely to receive HD aspirin and have a higher risk of developing VTE in general [90, 91]. The mechanical approach of thromboprophylaxis which is of utmost importance, includes the use of pneumatic compression devices or compression stockings. Our study did not account for the variations between the mechanical approach used in each study and the level of adherence to thromboprophylaxis protocols in each study which could be a source of heterogeneity. There are other sources of heterogeneity, namely the variations in study design, patient populations, definition of outcomes, and the differences of surgeon experience in studies [92].

We found the incidence of VTE after knee arthroplasty was significantly higher in HD aspirin rather than LD but not in hip arthroplasty. This finding may be associated with the following factors. The anatomical and physiological differences between the knee and hip joints might contribute to various responses to aspirin at different dosages, thus resulting in higher VTE incidents in TKA patients than THA [93, 94]. The anatomy of veins around the knee and hip joints are different, which may result in blood stasis and an increased risk of clot formation [93]. Knee arthroplasty might lead to more disturbed blood flow and stasis compared to hip arthroplasty, potentially impacting VTE risk [94]. TKA and THA involve different surgical techniques and trauma levels. The extent of tissue injury, the release of inflammatory mediators, and the overall surgical stress may vary, affecting the risk of thromboembolic events differently in knee and hip procedures. We suggest future studies report separate results for TKA and THA surgeries.

One of the complications of using aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) is GIB due to prostaglandin synthesis inhibition. Inhibition of COX-1 leads to decreased levels of prostaglandin, which is crucial to mucosal regeneration of the stomach lining [95]. The findings of the meta-analysis suggest that the dosage of aspirin taken may not affect the GIB incidents. Another systematic review demonstrated that The incidence of major bleeding events in the LD aspirin group

was not significantly different from the HD aspirin group [81].

We found the incidence of PJI after arthroplasty was higher in the HD aspirin group than in the LD aspirin group. Higher incidents of PJI in the HD group could mainly attributed to the anti-inflammatory and immunomodulatory effects of aspirin. As mentioned earlier, as the concentration of aspirin increases, it can inhibit both COX-1 and COX-2 and subsequently reduce the inflammatory mediators and cells [81, 82]. Thus, High doses of aspirin could potentially predispose patients to infectious agents and interfere with the immune response necessary for combating bacterial colonization and preventing PJI. In addition to its anti-inflammatory actions, aspirin has immunomodulatory effects, mainly on the maturation of antigen-presenting cells (APC), that could impact the host defense mechanisms against microbial pathogens [96, 97].

Theoretically, aspirin prescription could interfere with wound healing; the reason for that is aspirin acts as an anti-inflammatory agent, while in the initial phases of wound healing. To be more precise, macrophage activity is necessary in wound healing; studies have shown that lower doses of aspirin can have a beneficial effect in macrophages, modulating their anti-inflammatory response. While higher doses of aspirin have shown to be detrimental to wound healing [98]. Aspirin also inhibits the production of 12-hydroxyheptadecatrienoic acid, a molecule the promotes keratinocyte migration, which is required in the process of wound healing [99]. The risk of post-operative hematoma can also be increased in HD aspirin, since HD aspirin increases the risk of bleeding by inhibiting platelet aggregation. However, further studies are required to determine the specific interaction of aspirin with wound healing and post-operative hematoma formation in TKA and THA patients.In case of revision surgeries, some complications are more noteworthy; compared to other drugs, aspirin was considered a significantly better option for VTE prophylaxis [100]. However, the risks associated with aspirin, as it has the risk of bleeding, specifically GI bleeding, is not reversible, and might contribute to formation of hematoma and deter the wound healing process must be kept in mind.

Potential limitations

This study was limited by the inclusion of studies with low levels of evidence, and there is a need for more high-quality RCTs to fully comprehend the efficacy of aspirin prophylaxis following TJA. Nevertheless, many patients are needed in a randomized controlled trial to achieve sufficient statistical power because of the rare occurrence of symptomatic PE and DVT after total joint arthroplasty. Randomizing these patients may not always be ethical, as prophylactic treatment is frequently selected based on individual patient factors. Therefore, there may be an allocation bias when deciding on each patient's treatment. Future research needs to examine if there is a connection between patient comorbidities and demographics and the effectiveness of LD and HD aspirin. Additionally, there was a lack of data on potential major bleeding events and wound complications related to antiplatelet prophylaxis. Furthermore, future research needs to investigate potential issues like minor bleeding and specific blood transfusion requirements in patients who are prescribed aspirin. Last but not least, the majority of the included studies were conducted in the United States. Thus, the generalizability of our findings to broader populations and healthcare settings may be limited.

Conclusion

The findings suggest that LD aspirin may be a viable option for VTE chemoprophylaxis following TJA, potentially offering comparable efficacy with a lower risk of PJI compared to HD aspirin regimens. However, consideration should be given to anatomical and physiological differences, surgical techniques, and patient characteristics that may influence the observed outcomes.

Supplementary Information

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Supplementary Material 1

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P. M. analysed data and revised the final manuscript. MT.PF. wrote the initial draft and edited the final manuscript and prepared the tables and figures. A.A. and F.P and P.R contributed to the screening and data extraction and edited the final manuscript. All authors read and approved the final manuscript.

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