Abstract. – OBJECTIVE: Previous preliminary clinical trials have confirmed that edoxaban can be efficacious for venous thromboembolism (VTE). This meta-analysis was considered to evaluate edoxaban’s short-term efficacy and safety for venous thromboembolism after arthroplasty.

MATERIALS AND METHODS: A comprehensive search was performed in these databases: PubMed, MEDLINE, Web of Science, and EMBASE on March 2022. All eligible trials should be randomized controlled trials (RCTs) when evaluating short-term efficacy and safety outcomes of edoxaban for VTE after total hip or knee arthroplasty.

RESULTS: Nine RCTs with 4274 patients were involved in this meta-analysis. Edoxaban in the VTE group prevented the incidence of VTE and indicated valuable clinical efficacy. The incidence of adverse events (AEs) and adverse drug reactions (ADRs) in the edoxaban group was decreased than that in other groups. Edoxaban increased the incidence of all bleeding events. However, in the edoxaban group and other groups, there was no statistical difference between major bleeding events and clinically relevant non-major or minor bleeding events. Edoxaban subgroups included edoxaban 15 mg, edoxaban 30 mg and edoxaban 60 mg prevented the incidence of VTE. Edoxaban 30 mg and 60 mg group increased the risk of all bleeding events. Edoxaban 30 mg can increase the incidence of major bleeding events. There was no difference in clinically relevant non-major or minor bleeding events. Edoxaban 30 mg can decrease the incidence of AEs.

CONCLUSIONS: Edoxaban was an efficacious and safe option to prevent and treat VTE in patients undergoing arthroplasty. However, we need further trials to explore edoxaban’s long-term efficacy and safety.

Key Words: Edoxaban, Meta-analysis, Venous thromboembolism, Total hip, Knee arthroplasty.

Abbreviations
VTE: venous thromboembolism; RCTs: randomized controlled trials; PE: pulmonary embolism; VKA: vitamin K antagonist; UFH: unfractionated heparin; NOAC: new oral anticoagulants; AEs: adverse events; ADRs: adverse drug reactions.

Introduction
Venous thromboembolism (VTE) after undergoing total hip or knee arthroplasty is one of the most common dreadful complications. VTE is predominantly a disease of older age and is rare before sexual maturity. Considered a successful procedure, total hip or knee arthroplasty can improve patients’ quality of life. Orthopedic surgeons need to focus on the prevention of postoperative complications after surgery.
An epidemiology survey demonstrated that the VTE is estimated to be from 1.04% to 1.83% per year in the USA, rates that are like to that of stroke. Reported incidence rates for pulmonary embolism (PE) (with or without DVT), and for DVT alone (without PE), range from 0.29% to 0.78% and 0.45% to 1.17% one year in the USA, respectively. The overall age-adjusted annual incidence rate is increased to 1.3% in men vs. 1.1% in women. VTE is a complex, multifactorial disease, which involves interactions between acquired predispositions to thrombosis and various risk factors. Major risk factors for incident VTE were surgery, active cancer, neurological disease with leg paralysis, trauma fracture, and pregnancy. According to the American Society of Anesthesiology, criteria are risk factors for VTE after total hip arthroplasty, including other factors like obesity and poor physical status.

VTE recurs frequently, with estimating approximate 30% of which will relapse within 10 years. The reported recurrence rates for VTE, DVT, and PE were 2.9%, 8.5%, and 22% respectively. Due to VTE prevention, physical therapies are usually applied for VTE prevention, such as the two lower extremities’ power pumps that enhance muscle contraction. Moreover, oral thrombosis and diffusion inhibitor drugs are also basic options for prevention. According to the evidence-based guideline to prevent VTE, we must select the ideal prophylactic regimen. The common anticoagulants include vitamin K antagonist (VKA), unfractionated heparin (UFH), low molecular weight heparin (LMWH), and new oral anticoagulants (NOAC). LMWH is a classic drug to prevent VTE after orthopedic surgery and NOAC includes factor Xa inhibitors and direct thrombin inhibitors. Apixaban and Rivaroxaban were widely used in the prevention of postoperative venous thrombosis. The route of administration is more advantageous because it cannot be affected by food intake and the interaction with other drugs. Nowadays, edoxaban is approved for arthroplasty in Japan, Europe, the United States, Canada, Australia, and China. Though edoxaban is becoming the latest anticoagulant in VTE prevention, it leads to a prominent clinical problem: how is the short-term efficacy and safety of edoxaban in the patients after total hip or knee arthroplasty? We conducted a meta-analysis using edoxaban as an anticoagulant to answer the problem. The first analysis focuses on short-term efficacy and the incidence of VTE. The second analysis focuses on safety including all bleeding events, major bleeding events, clinically relevant non-major or minor bleeding events, adverse events, and adverse drug events.

Materials and Methods

Ethics Statement

The ethical statement was unnecessary as the data of this study was extracted from previously published articles.

Data Sources and Search Strategy

Papers on edoxaban treating VTE were searched from the databases in March 2022, including PubMed, MEDLINE (through PubMed), Web of Science (science and social science citation index), and EMBASE. We used a series of logic combinations and search terms related to the topic (“edoxaban”, “venous thromboembolism”, “total hip or knee arthroplasty”) to perform searches in each database. Published systematic reviews of the same topic are reviewed as potential candidate trials. An example of a searching strategy for PubMed was as follows: (“edoxaban tosylate” [MeSH Terms] OR “edoxaban” [All Fields] OR “Savaysa” [All Fields]) AND (“venous thromboembolism” [MeSH Terms]) AND (“arthroplasty, replacement, hip” [MeSH Terms] OR “total hip arthroplasty” [All Fields] OR “arthroplasty, replacement, knee” [MeSH Terms] OR “total knee arthroplasty” [All Fields]).

Trial Selection

Two reviewers performed an initial screening of the literature by checking titles and abstracts after removing duplicates. The eligibility of the trials was assessed by reviewing the full text. Authors were consulted when there was uncertainty for example whether different publications are from the same trial. Disagreements were resolved by discussion and the third reviewer was consulted.

All eligible trials should meet the following inclusion criteria:

(1) double-blinded, randomized controlled trials (RCTs);
(2) patients receiving total hip or knee arthroplasty;
(3) trials compared edoxaban to placebo or other anticoagulants or physiotherapy for VTE prevention;

Exclusion criteria should be as follows:

(1) non-RCTs;
(2) trials lacking standard treatment or use of a dose are not approved by the drug regulatory
agency of the country where the research is located;
(3) trials with insufficient data for the evaluation of VTE efficacy and safety outcomes.

Data Extraction and Quality Assessment
Two reviewers collected and assessed the eligibility of 22 trials after duplicates were removed by viewing the title, abstract, and the whole paper. Most trials were eliminated after screening the title or abstract based on the inclusion or exclusion criteria. Once trials that meet the inclusion criteria were identified, two reviewers would assess quality using Jadad Scale. Once quality was established, independent data extraction would be performed by at least two researchers using a standardized extraction form and comparing their findings to ensure data accuracy.

Risk of Bias Assessment
Two reviewers independently assessed the risk by using the Cochrane risk of bias tool for randomized trials. Areas of bias included random sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting risk. The risk of each area of risk was categorized as low, unclear, and high. Disagreements were resolved by consultation with a third reviewer or through discussion.

Outcome Measures
Our short-term efficacy outcomes were the incidence of VTE, including lower limb DVT confirmed by bilateral venography, diagnosis of symptomatic PE confirmed by radiological examination, or symptomatic DVT confirmed before venography. Safety outcomes were the combination of all bleeding events, major bleeding events, clinically relevant non-major or minor bleeding events, adverse events (AEs), and adverse drug events. Outcomes were derived from each trial’s treatment period, which varied from 7 to 90 days. Major bleeding events were defined as life-threatening bleeding, bleeding into critical organs (retroperitoneal, intracranial, intraocular, or intraspinal), clinically significant bleeding resulting in a decrease in hemoglobin of >2 g/dL or transfusion of >4 units (1 unit = approximately 200 mL) of blood or required repeat surgery. Clinically relevant non-major or minor bleeding events were defined as those that did not meet the criteria for major bleeding but were associated with hema-

coma (at least 5 cm long), epistaxis or gingival bleeding (at least 5 min), gastrointestinal bleeding, gross hematuria (persistent 24 h after onset) or another bleeding that was assessed as clinically significant.

Statistical Analysis
Review Manager 5.4.1 (The Cochrane Collaboration, Oxford, United Kingdom) was applied for meta-analysis. For continuous data, pooled mean difference (MD) with 95% confidence interval (CI) was calculated, while for dichotomous data, relative risk (RR) with 95% CI was calculated. Egger’s test was used to identify publication bias. Clinical heterogeneity was appraised by the reviewers with a background in VTE clinical experience. Statistical heterogeneity was assessed with the inference of $I^2$. If the $I^2$ value was greater than 50%, a random model would be applied. Otherwise, $I^2$ value was less than 50%, a fixed model would be applied. Sensitivity analysis was performed by excluding studies with a high overall risk of bias. All analyses were carried out in Stata 12.0 (The Cochrane Collaboration, College Station, TX, USA). The significance level was set at $p < 0.05$.

Results

Trial Selection Process
In the initial literature search, 22 records were identified. After the removal of duplicates and selection based on eligibility criteria, 9 RCTs were included in this meta-analysis15-23. The procession was described in the PRISMA flow diagram in Figure 1.

Trial Characteristic
All studies started in 2010 and ending in 2018, belonging to an eight-year span, and all of them were RCTs. The total number of participants in these studies was 2579 patients treated with edoxaban and 1695 patients treated with other drugs or placebo. The location of the surgery was knee and hip. Most of the treatment period ranged from 7 days to 14 days, and one of them was 90 days. The concrete trial characteristic was shown in Table I.

Risk of Bias Assessment of the Included Trials
The assessment was conducted by two reviewers independently using the Cochrane risk
of bias tool for randomized trials. Random sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting risk were included as main bias. The risk of each bias domain will be graded as low, unclear and high. Disagreements were resolved by consulting a third reviewer or through discussion. As presented in Figure 2, the study quality of these included trials was relatively high.

**Short-Term Efficacy Outcome**

**Edoxaban on VTE**

In this trial, the anticoagulant efficacy of edoxaban was evaluated by the incidence of VTE events as the primary outcome. As shown in Figure 3A, edoxaban on VTE illustrated a statistically significant difference between edoxaban and control (n=4045, RR=0.49, p<0.00001). According to the results of the meta-analysis, we can conclude that edoxaban has better efficacy than
Table I. Basic characteristics of the included trials.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Treatment Duration</th>
<th>Location of surgery</th>
<th>Regimen</th>
<th>Numbers of patients</th>
<th>Age</th>
<th>Gender (Female%)</th>
<th>Control</th>
<th>Numbers of patients</th>
<th>Age</th>
<th>Gender (Female%)</th>
<th>Observation index</th>
<th>Modified Jadad Score (7-point)</th>
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</thead>
<tbody>
<tr>
<td>Fuji, T et al15</td>
<td>2010</td>
<td>11-14 days</td>
<td>Knee</td>
<td>Edoxaban 15 mg</td>
<td>103</td>
<td>70.1 ± 8.7</td>
<td>76.7</td>
<td>Placebo q.d.</td>
<td>102</td>
<td>70.6 ± 6.8</td>
<td>76.5</td>
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<td>Edoxaban 5 mg</td>
<td>106</td>
<td>71.8 ± 6.9</td>
<td>83</td>
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<td>Edoxaban 15 mg</td>
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<td>71.4 ± 8.2</td>
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<td>Edoxaban 30 mg</td>
<td>106</td>
<td>71.7 ± 7.1</td>
<td>80.2</td>
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<tr>
<td>Gary Raskob et al16</td>
<td>2010</td>
<td>7-10 days</td>
<td>Hip</td>
<td>Edoxaban 15 mg</td>
<td>193</td>
<td>57.3 ± 12.46</td>
<td>58.5</td>
<td>Dalteparin 5000 IU q.d.</td>
<td>175</td>
<td>57.6 ± 12.41</td>
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<td>Edoxaban 30 mg</td>
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<td>Edoxaban 60 mg</td>
<td>187</td>
<td>58.3 ± 11.55</td>
<td>63.6</td>
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<td>2014</td>
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<td>Knee</td>
<td>Edoxaban 15 mg</td>
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<td>74.6 ± 0.63</td>
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<tr>
<td>Fuji T et al18</td>
<td>2014</td>
<td>11-14 days</td>
<td>Hip</td>
<td>Edoxaban 15 mg</td>
<td>89</td>
<td>61.3 ± 10.3</td>
<td>80.8</td>
<td>Enoxaparin 2000 IU (20 mg) b.i.d.</td>
<td>89</td>
<td>58.9 ± 10.7</td>
<td>79.7</td>
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<td>Edoxaban 30 mg</td>
<td>86</td>
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<td>95.8</td>
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<td>Takeshi Fuji et al19</td>
<td>2015</td>
<td>11-14 days</td>
<td>Hip</td>
<td>Edoxaban 30 mg</td>
<td>307</td>
<td>62.8 ± 9.61</td>
<td>86.3</td>
<td>Enoxaparin 2000 IU t.i.d.</td>
<td>303</td>
<td>62.8 ± 9.72</td>
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<td>Edoxaban 30 mg</td>
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<td>Izushi Y et al20</td>
<td>2016</td>
<td>14 days</td>
<td>Knee</td>
<td>Edoxaban 30 mg</td>
<td>667</td>
<td>68.3 ± 8.4</td>
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<td>Fondaparinux 2.5 mg q.d.</td>
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<tr>
<td>Yohko Kawai et al21</td>
<td>2016</td>
<td>11-14 days</td>
<td>Hip or Knee</td>
<td>Edoxaban 30 mg</td>
<td>19</td>
<td>71.3 ± 8.7</td>
<td>84.2</td>
<td>Enoxaparin 2000 IU (20 mg) t.i.d.</td>
<td>19</td>
<td>74.1 ± 7.1</td>
<td>89.5</td>
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<tr>
<td>Daisuke Sueta et al22</td>
<td>2018</td>
<td>7 days</td>
<td>Knee</td>
<td>Edoxaban 60 mg</td>
<td>55</td>
<td>72.7 ± 9.1</td>
<td>81.4</td>
<td>Physiotherapy</td>
<td>29</td>
<td>71.9 ± 8.0</td>
<td>96.7</td>
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<td>Mochizuki Takeshi et al23</td>
<td>2018</td>
<td>90 days</td>
<td>Hip or Knee</td>
<td>Edoxaban 60 mg</td>
<td>55</td>
<td>72.7 ± 9.1</td>
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<td>71.9 ± 8.0</td>
<td>96.7</td>
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① Numbers of Venous thromboembolism (VTE);
② Numbers of all bleeding events;
③ Numbers of major bleeding events;
④ Numbers of clinically relevant non-major or minor bleeding events;
⑤ Adverse events (AEs);
⑥ Adverse drug reactions (ADRs)
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control in preventing VTE after arthroplasty from the forest plot.

The secondary results of the meta-analysis on the efficacy of edoxaban were as follows: the meta-analysis of edoxaban on VTE displayed a statistically significant difference between edoxaban subgroups included edoxaban 15 mg, edoxaban 30 mg and edoxaban 60 mg (n=1,054, RR=0.68, \(p=0.0004\); n=2,784, RR=0.52, \(p=0.001\); n=570, RR=0.27, \(p=0.0001\)) and respective control (Figure 3B-3D).

**Safety Outcome**

**Edoxaban on all bleeding events**

As shown in Figure 4A, the incidence of all bleeding events in edoxaban was significantly increased than in control (n=3,745, RR=1.43, \(p=0.008\)). From the forest plot, we can conclude that the edoxaban was increased compared to the control in terms of all bleeding events. These results indicated that edoxaban has no significant advantage over other drugs in preventing all bleeding events.

Secondary results of the meta-analysis on the efficacy of edoxaban were as follows: the incidence of all bleeding events in edoxaban 30 mg and 60 mg (n=2,784, RR=1.35, \(p=0.03\); n=570, RR=3.23, \(p=0.003\)) was increased than respective control, but there was no significant statistical difference between edoxaban 15 mg and control (Figure 4B-4D).

**Edoxaban on major bleeding events**

As shown in Figure 5A, there was no statistical difference between edoxaban and control in the incidence of major bleeding events (n=3,714, RR=1.41, \(p=0.08\)). According to the results of the meta-analysis, we can conclude the forest plot: in terms of major bleeding events, edoxaban had no statistical difference from control. There was no significant difference between edoxaban and the other drugs in terms of major bleeding events.

Secondary results of the meta-analysis on the efficacy of edoxaban were as follows: the meta-analysis of edoxaban on major bleeding events demonstrated that there was no statistical difference between edoxaban subgroups including edoxaban 15 mg and edoxaban 60 mg (n=576, RR=2.72, \(p=0.54\); n=570, RR=2.85, \(p=0.36\)) and respective control. These results illustrated that edoxaban 30 mg can increase the risk in terms of major bleeding events (Figure 5B-5D).

**Edoxaban on clinically relevant non-major or minor bleeding events**

As shown in Figure 6A, there was no statistical difference between edoxaban and control in the incidence of clinically relevant non-major or minor bleeding events (n=3,359, RR=1.34, \(p=0.23\)). According to the results of the meta-analysis, we can conclude that in terms of clinically relevant non-major or minor bleeding events, edoxaban did not increase the risk in clinically relevant non-major or minor bleeding events than other drugs.

Secondary results of the meta-analysis on the efficacy of edoxaban were as follows: the meta-analysis of edoxaban on clinically relevant non-major or minor bleeding events in-
dicated that there was no statistical difference between edoxaban subgroups including edoxaban 15 mg, edoxaban 30 mg, and edoxaban 60 mg (n=576, RR=1.37, p=0.60; n=2,487, RR=1.36, p=0.22; n=570, RR=1.59, p=0.43) and respective control. Edoxaban subgroups did not increase the risk of clinically relevant non-major or minor bleeding events (Figure 6B-6D).

**Edoxaban on adverse events (AEs)**

As shown in Figure 7A, there was a statistical difference between edoxaban and control in the incidence of adverse events (n=2,456, RR=0.85, p=0.01). According to the results of the meta-analysis, we can conclude that in terms of AEs, edoxaban had an advantage over other drugs.

Secondary results of the meta-analysis on the efficacy of edoxaban were as follows: the meta-analysis of edoxaban on AEs indicated that there was a significant statistical difference between edoxaban 30 mg and control (n=2141, RR=0.86, p<0.0001). It indicated that edoxaban 30 mg can reduce the incidence of adverse events (AEs) than other drugs. (Figure 7B)
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Edoxaban on adverse drug reactions (ADRs)

As shown in Figure 8, there was a statistical difference between edoxaban and enoxaparin in the incidence of adverse drug reactions (n=428, RR=0.67, p<0.00001). According to the results of the meta-analysis, we can conclude the forest plot: In terms of ADRs, edoxaban 30 mg had an advantage over enoxaparin 2000 IU.

Publication Bias Test

Stata 12 software was used to carry out Egger’s test and the result indicated that there was no obvious publication bias between edoxaban and control in VTE (p=0.42), all bleeding events (p=0.122), major bleeding events (p=0.556), clinically relevant non-major or minor bleeding (p=0.237), and adverse events (p=0.07). It indicated that the included trials were more representative.

Discussion

As compared to control, edoxaban reduced the incidence of VTE after arthroplasty (Figure 2). In contrast, edoxaban increased all bleeding events (including major and clinically relevant non-major or minor bleeding events) (Figures 3, 4, 5). However, edoxaban protected against adverse events and adverse drug reactions rather than control (Figure 6, 7).
The edoxaban subgroup analyses on VTE showed that the RR (95 %CI) of edoxaban subgroup was 15 mg 0.68 (0.54-0.84), 30 mg 0.52 (0.35-0.77), 60 mg 0.27 (0.14,0.52). In terms of our meta-analyses, edoxaban also protected against VTE after arthroplasty. What’s more, the short-term efficacy of edoxaban had more advantages than other drugs (dalteparin, enoxaparin, fondaparinux, enoxaparin, fondaparinux, apixaban).

VTE is one of the common complications after arthroplasty. Clinical prediction rules for post-operative VTE would allow orthopedists to select thromboprophylaxis based on VTE24. Kulshrestha et al25 concluded that patients undergoing TKA could be prospectively identified as being at low risk of VTE and that they should be treated with aspirin instead of anticoagulant postoperatively. Although the method could reduce the incidence of postoperative hemorrhage, aspirin is still one of the classically effective drugs in preventing VTE after arthroplasty26,27. In recent years, new oral anticoagulants have gradually entered clinical applications. Clinical practice guidelines recommend the use of rivaroxaban 10 mg q.d. or apixaban 2.5 mg b.i.d or dabigatran etexilate 220 mg q.d. for the prevention of DVT after arthroplasty28. Edoxaban is a selective inhibitor of coagulation factor...
Short-term efficacy and safety of edoxaban for venous thromboembolism after total hip or knee arthroplasty

Xa, which can inhibit free FXa and prothrombin activity, thrombin-induced platelet aggregation, and thrombus formation.

In terms of safety, 5 indicators were observed, which were all bleeding events, major bleeding events, clinically relevant non-major bleeding events, adverse events, and adverse drug reactions. In all bleeding events, the results from our meta-analysis indicated no significant difference (Figure 3). However, higher rates occurred in all bleeding events of the edoxaban subgroup 30 mg and 60 mg. The RR (95 %CI) of edoxaban subgroups were 15 mg 1.63 (0.76-3.48), 30 mg 1.35 (1.04,1.77), 60 mg 3.23 (1.51,6.91). It suggested that an adequate dosage of edoxaban to prevent VTE may increase the incidence of bleeding events. In major bleeding events, the results indicated no significant statistical difference (Figure 4). While there was also no significant statistical difference in the edoxaban subgroup 15 mg and 60 mg. However, high rates occurred in major bleeding of the edoxaban subgroup 30 mg. The RR (95 %CI) of edoxaban subgroups were 15 mg 2.72 (0.11-66.38), 30 mg 1.50 (1.01, 2.21), 60 mg 3.23 (0.30, 27.20). The subgroup indicated that recommended dosage of edoxaban 60 mg also increased the risk of major bleeding events. The result was consistent with the clinical trial results29. In clinically relevant non-major or minor bleeding events, the results indicated no significant statistical difference (Figure 5). There was also no significant statistical difference be-
between edoxaban subgroups of 15 mg, 30 mg, and 60 mg. The RR (95% CI) of edoxaban subgroups were 15 mg 1.37 (0.42-4.50), 30 mg 1.36 (0.83, 2.23), 60 mg 1.59 (0.50, 5.05). In adverse events, the results showed a statistical difference (Figure 6), which indicated that edoxaban can reduce the incidence of adverse events. Nagaoki et al.30 used edoxaban for treating portal vein thrombosis with liver cirrhosis and they found that edoxaban efficacy was better than warfarin. There was also a significant difference in the edoxaban subgroup 30 mg. The RR (95% CI) of edoxaban subgroup was 30 mg 0.86 (0.81, 0.91). In adverse drug reactions, the results indicated a significant difference between edoxaban 30 mg and enoxaparin 2000 IU (Figure 7).

However, this meta-analysis still has several limitations. First, compared to the previous review, the numbers of included trials are relatively small. However, the quality of these trials is excellent, and the number of subjects involved is adequate. In addition, a minimum threshold for the number of included trials has not been established.11 Second, the treatment strategies and baseline characteristics of patients in the included trials are inconsistent. For instance, ethnicity and regions are different across these trials. Third, the dosage and duration vary among included trials. Forth, while selecting different sorts of anticoagulants for control, we need to compare different anticoagulants with different dosages of edoxaban to make sure edoxaban efficacy and safety. Fifth, in this review, only one trial (Fuji et al.19) reports adverse drug reactions. We could not use a publication bias test to identify the adverse drug events in edoxaban, but there is no existing evidence indicating that edoxaban will increase the incidence of adverse drug events. The insufficient adverse drug events may interfere with the result and add heterogeneity to some results. Therefore, the current results should

Figure 7. A, Forest plot for comparison of adverse events between edoxaban and control. B, Comparison of adverse events between edoxaban subgroup 30 mg and control.

Figure 8. Forest plot for comparison of adverse drug reactions between edoxaban 30 mg and enoxaparin 2000 IU.
be treated with caution. Finally, additional trials should be conducted to further evaluate the long-term efficacy and especially the safety of edoxaban in the treatment of VTE after arthroplasty. Hence, multiple trials should be taken to find out the safety outcome of edoxaban.

Conclusions

The administration of 30/60 mg edoxaban significantly reduces the risk of VTE after total hip arthroplasty or total knee arthroplasty. However, the recommended dosage will increase the risk of bleeding, which remind us to monitor coagulation indicators. Despite higher rates of bleeding, edoxaban cannot increase adverse events and adverse drug events. The meta-analysis indicated that edoxaban as an oral anticoagulant may be an effective medicine to prevent and treat venous thromboembolism after undergoing total hip or knee arthroplasty. However, we need further trials to examine edoxaban’s long-term efficacy and safety.

 Availability of Data and Materials
All data generated or analyzed during this study are included in this published article.

Authors’ Contributions

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Ethics Approval and Consent to Participate
The ethical statement was unnecessary as the data of this study were extracted from previously published articles.

Consent for Publication
Not applicable.

Conflict of Interest
The authors have no conflicts of interest to disclose.

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References
10) Mont MA, Jacobs JJ. AAOS clinical practice guideline: preventing venous thromboembolic disease


