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REVIEW

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Efficacy and safety of direct oral anticoagulants versus low-molecular-weight heparin for thromboprophylaxis after cancer surgery: a systematic review and meta-analysis

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Abstract

Background Direct oral anticoagulants (DOACs) used as an alternative to low-molecular-weight heparin (LMWH) for thromboprophylaxis after cancer surgery for venous thromboembolic events (VTE) remains unclear. This study aimed to investigate the efficacy and safety of DOACs versus LMWH in these patients.

Materials and methods A search of EMBASE, MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science was carried out and included all randomized controlled trials (RCTs) and observational studies that directly compared DOACs with LMWH for thromboprophylaxis in patients after cancer surgery through July 25, 2023. The primary efficacy and safety outcomes were VTE, major bleeding, and clinically relevant non-major bleeding (CRNMB) within 30 days of surgery. The risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB2) tool for RCTs and ROBINS-I tool for non-randomized studies. This study was registered in PROSPERO (CRD42023445386).

Results We retrieved 5149articles, selected 27 for eligibility, and included 10 studies (three RCTs and seven observational studies) encompassing 3054 patients who underwent postoperative thromboprophylaxis with DOACs (41%) or LMWH (59%). Compared to LMWH thromboprophylaxis, DOACs had a comparable risk of VTE (RR:0.69[95% CI:0.46–1.02], $I^2 = 0\%$), major bleeding (RR:1.55 [95% CI:0.82–2.93], $I^2 = 2\%$), and CRNMB (RR, 0.89 [95% CI, 0.4–1.98], $I^2 = 31\%$) during the 30-day postoperative period. Subgroup analysis of VTE and major bleeding suggested no differences according to study type, extended thromboprophylaxis, tumor types, or different types of DOAC.

Conclusion DOACs are potentially effective alternatives to LMWH for thromboprophylaxis in patients undergoing cancer surgery, without increasing the risk of major bleeding events.

Keywords Cancer surgery, Direct oral anticoagulants, Low-molecular-weight heparin, Meta-analysis, Thromboprophylaxis

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Introduction

Venous thromboembolic events (VTEs), including deep vein thrombosis (DVT) and pulmonary embolism (PE), remain major causes of morbidity and mortality in patients with cancer [1]. Patients with cancer increased sevenfold risk of venous thrombosis compared with non-cancer patients (odds ratio [OR], 6.7; 95% confidence interval [CI], 5.2–8.6) [2]. Surgical trauma increases the risk of developing VTE. This increased twofold risk of VTE in patients with known cancer vs. non-cancer patients undergoing the same surgery [3]. Education for the risk assessment and prophylaxis of VTE and considering guidelines are important for making the optimal thromboprophylaxis decision [4]. Current guidelines [5–8] recommend the use of VTE prophylaxis with 7–10 days of low-molecular-weight heparin (LMWH) or unfractionated heparin in patients who underwent cancer-related surgery, and 4 weeks extended-duration LMWHs prophylaxis for abdominal-pelvic surgery because of the significantly reduced incidence of VTE without increasing bleeding complications or mortality [9, 10].

However, the use of subcutaneous low-molecular-weight heparin has some limitations such as injection site reaction, pain, bruising, and bleeding, which may impair the quality of life of patients [7]. Patients taking apixaban demonstrated good adherence, with significantly increased adherence from 3 to 25% compared with enoxaparin [11]. Currently, the use of DOACs as an effective and safe option for the treatment of cancer-associated thrombosis in selected cancer patients has been supported by the results of several high-quality randomized controlled trials (RCTs) [6, 12–16] and is strong recommended in guidelines [17–20]. However, evidence to support the use of direct oral anticoagulants as an alternative to LMWH for the prophylaxis of postoperative VTE in patients with cancer is insufficient. Recently, three randomized clinical trials showed evidence for the safety and efficacy of two direct oral anticoagulants for extended thromboprophylaxis of malignant neoplasms after surgery [5, 21, 22], and apixaban and rivaroxaban were weakly recommended as options for extended pharmacological thromboprophylaxis after cancer surgery [17].

Therefore, we present the results of a systematic review and meta-analysis of all RCTs and observational studies comparing the efficacy and safety of DOACs and LMWH for postoperative VTE prophylaxis in cancer patients undergoing surgery.

Materials and methods

This work was reported in line with the PRISM, Supplementary file 1 (Preferred Reporting Items for Systematic Reviews and Meta-Analysis)2020 [23] and AMSTA, Supplementary file 2 (Assessing the Methodological Quality of systematic reviews) Guidelines [24]. The systematic review protocol and search strategy were registered in the PROSPERO International Prospective Register of Systematic Reviews (ID number and hyperlink: CRD42023445386).

Search strategy

We conducted a systematic literature search using EMBASE (1947 to July 25, 2023), MEDLINE via PubMed (1946 to July 25, 2023), the Cochrane Central Register of Controlled Trials (CENTRAL, searched July 25, 2023), and Web of Science (1985 to July 25, 2023), and searched www.clinicaltrials.gov for completed and ongoing research, as well as references of narrative reviews, and included trials from all languages through July 25, 2023. The complete search strategy is available in Supplementary Table 1.

Inclusion and exclusion criteria

We included articles that included conference abstracts if they met the following criteria: (1) randomized controlled trials (RCTs) and observational studies; (2) adult patients (18 years old or older) who underwent cancer-related surgery; (3) directly compared DOAC (dabigatran, rivaroxaban, apixaban, betrixaban, or edoxaban) to LMWH (dalteparin, enoxaparin, tinzaparin, or nadroparin) for thromboprophylaxis; and (4) reported primary efficacy or safety outcomes. The meta-analysis excluded case reports, review articles, descriptive articles, animal trials, non-cancer surgery, non-comparative observational studies, not DOACs vs. LMWH, and lacking the outcomes of interest.

Outcome measures

The primary efficacy outcome was VTE, defined as asymptomatic or symptomatic DVT of the lower extremity with or without PE, reported within the 30-day postoperative period. The primary safety outcome was major bleeding and clinically relevant non-major bleeding (CRNMB), defined according to the International Society on Thrombosis and Haemostasis [8, 25].

Data extraction and risk of bias assessment

Two investigators (HZ and TTC) independently selected the title and abstract, and extracted the data. Discrepancies were resolved by consensus and were reviewed by a third investigator. The quality of RCTs was identified using the Cochrane Risk of Bias 2 (RoB2) tool [26] and observational studies were assessed using the Risk of Bias in Non-randomized Studies (ROBINS-I) Tool [27] independently by two investigators (HZ and TTC). The RoB2 tool assesses five domains: adequacy of the randomization

process, deviations from intended interventions, missingness of outcome data, measurement of the outcome, and selection of the reported result. The ROBINS-I tool assesses seven domains: confounding, selection of participants, classification of intervention, deviations from intended intervention, missing data, measurement of outcomes, and selection of the reported result.

Statistical analysis

Forest plots of comparative relative risk (RR) and 95% confidence of primary efficacy and safety outcomes were calculated and pooled using the Mantel–Haenszel random effects model in Revman 5.3 software [28]. Heterogeneity across the trials was assessed using Cochran's Q test and the I^2 statistic [29]. Subgroup analyses were performed according to study design (RCTs versus observational studies), extended thromboprophylaxis, and different tumor types. Sensitivity analyses were conducted to determine the robustness of the results by using the leave-one-out method. We did not evaluate publication bias because fewer than ten studies reported primary efficacy or safety outcomes [30].

Results

Study selection and characteristics

A total of 5149 articles were identified and screened for titles and abstracts, and 27 full-text articles were selected for eligibility. A detailed screening process is presented below in the form of a PRISMA flow diagram produced by the tool [31] (Fig. 1). A total of 10 studies (three RCTs [21, 22, 32] and 7observational studies [33–39]), encompassing 3054patients, were included in the systematic review. Of the 10 studies, eight (three RCTs [21, 22, 32] and five observational studies [34, 36–39]) were included in the pooled analysis comparing the efficacy and safety of thromboprophylaxis after cancer surgery within 30 days. The types of cancer included gynecological malignancies ($n=5$), urological malignancies ($n=3$), Pancreatic adenocarcinoma ($n=1$) and lung cancer ($n=1$). The included studies used rivaroxaban ($n=4$), apixaban ($n=4$), and dabigatran ($n=1$); one observational study used these three drugs. The characteristics of the included studies are summarized in Table 1.

Risk of bias

Two of the three randomized controlled trials were adjudicated to a low risk of bias [21, 32] and one had some concern because the trial was stopped due to a lower-than-expected event rate [22] (Fig. 2A). All seven observational studies had at least a moderate risk of bias due to confounding of the effect of intervention in this study, such as the type and duration of surgery, age and the presence of other VTE risks. 3 observational studies [33, 36, 37] were adjudicated to a moderate risk of confounding bias by using a multivariate logistic regression

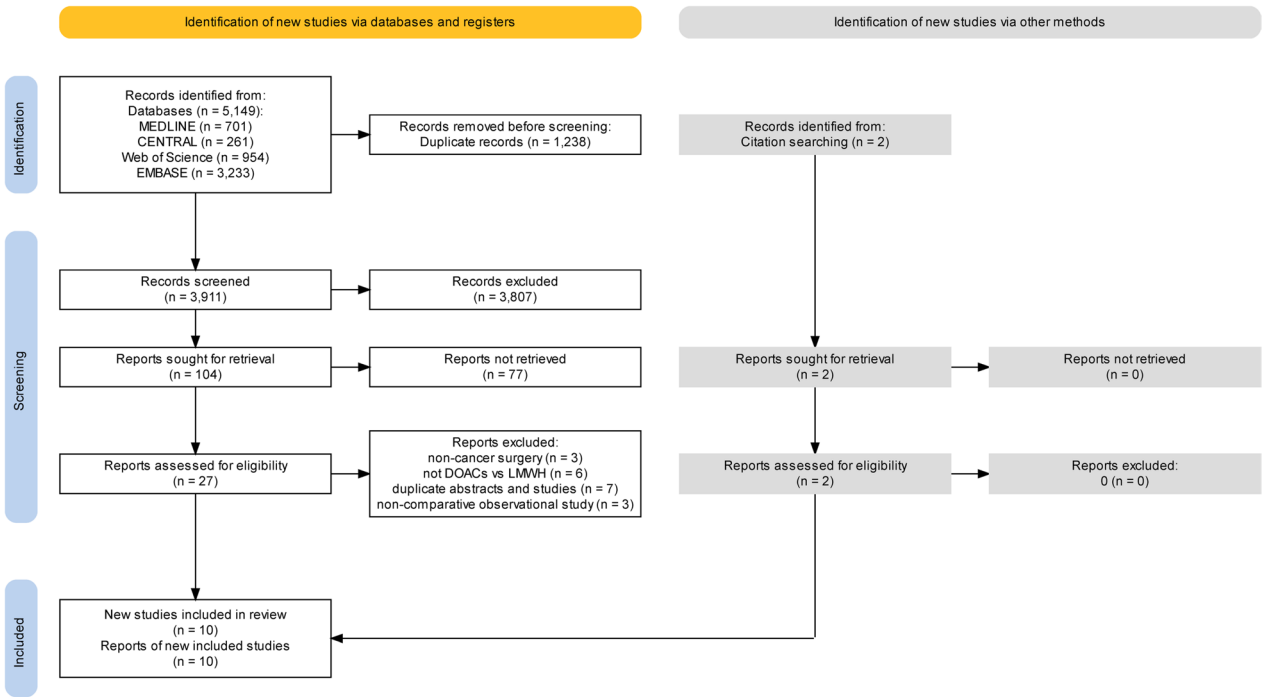

Fig. 1 PRISMA flowchart

Table 1 Summary of studies from systematic review of DOAC vs. LMWH for thromboprophylaxis after cancer-related surgery

Study	Publication Type	Design	Median age(years)[a]	Male[a]%	Malignancy Type	Study Size[a]	Intervention		Outcomes		
							DOAC	LMWH	Endpoint (time)	DOAC	LMWH
Guntupalli 2020 [21]	Full-Text	RCT	58/58.5	0	Gynecologic malignancy	204/196	Apixaban	Enoxaparin	VTE (90 days) MB(30 days) CRNMB(30 days) Readmission (30 days)	1%(2/204) 0.5%(1/204) 5.9%(12/204) 2.9%(6/204)	1.5%(3/196) 0.5%(1/196) 9.7%(19/196) 2.6%(5/196)
Oliveira 2022 [22]	Full-Text	RCT	54/56	0	Gynecologic malignancy	114/114	Rivaroxaban	Enoxaparin	VTE(30 days) MB(30 days) CRNMB(30 days)	3.5%(4/114) 0%(0/114) 0%(0/114)	4.4%(5/114) 0%(0/114) 2.6%(3/114)
Zhao 2023 [32]	Full-Text	RCT	61.2/61.7	53.5/47.3[b]	Lung cancer	200/203	Rivaroxaban	nadroparin	VTE(30 days) MB(30 days) CRNMB(30 days)	12.5%(25/200) 9.7%(19/196) 2.5%(5/196)	17.7%(36/203) 6.5%(13/201) 0.5%(1/201)
Nagy 2018 [33]	Abstract	Observational study	NR	0	Gynecologic malignancy	147/451	Rivaroxaban	LMWH	VTE (90 days) bleeding complications(NR)	0.7%(1/147) 2%(3/147)	2.4%(11/451) 0.7%(3/451)
Spénard 2023 [37]	Full-Text	Observational study	60/63	0	Gynecologic malignancy	112/144	Apixaban	Enoxaparin	VTE(30 days) MB(30 days) Readmission (30 days)	3%(3/112) 0%(0/112) 6%(7/112)	4%(6/144) 0%(0/144) 5%(7/144)
Swaroop 2021 [38]	Abstract	Observational study	NR	0	Gynecologic malignancy	82/233	Rivaroxaban	LMWH	VTE (30 days) VTE (90 days) MB (30 days)	1.2%(1/82) 2.4%(2/82) 3.7%(3/82)	1.7%(4/233) 4.3%(10/233) 0.4%(1/233)
Rashid 2018 [35]	Full-Text	Observational study	NR	59	Pancreatic adenocarcinoma	87/12	dabigatran	Enoxaparin	MB (90 days) Minor bleeding(90 days)	4.5%(4/87) 2.3%(2/87)	0%(0/12) 0%(0/12)
Rich 2023 [36]	Full-Text	Observational study	69/69	82/76	Bladder cancer	124/250	Apixaban	Enoxaparin	VTE (30 days) MB (30 days) Readmission (30 days) Mortality (30 days)	1.6%(2/124) 0.8%(1/124) 20%(25/124) 0.8%(1/124)	3.2%(8/250) 0.4%(1/250) 19%(48/250) 1.6%(4/250)
Westerman 2022 [39]	Full-Text	Observational study	66/66	84/79	Urological malignancy	154/161	Apixaban	Enoxaparin	VTE(30 days) MB(30 days) CRNMB(30 days)	0%(0/154) 0%(0/154) 3.9%(6/154)	1.7%(3/161) 1.2%(2/161) 4.3%(7/161)
Ortiz 2021 [34]	Full-Text	Observational study	65/68	69/70	Bladder cancer	29/37	Rivaroxaban (83%), Apixaban(14%) and Dabigatran(3%)	Enoxaparin	VTE(30 days) VTE(90 days) CRNMB(30 days) Readmission (30 days)	0%(0/29) 3.4%(1/29) 3.4%(1/29)	0%(0/37) 8.1%(3/37) 0%(0/37)

RCT randomized controlled trial, *NR* not reported, *VTE* venous thromboembolism, *MB* major bleeding, *CRNMB* clinically relevant non-major bleeding

[a] Presented as DOAC/LMWH groups

[b] Median

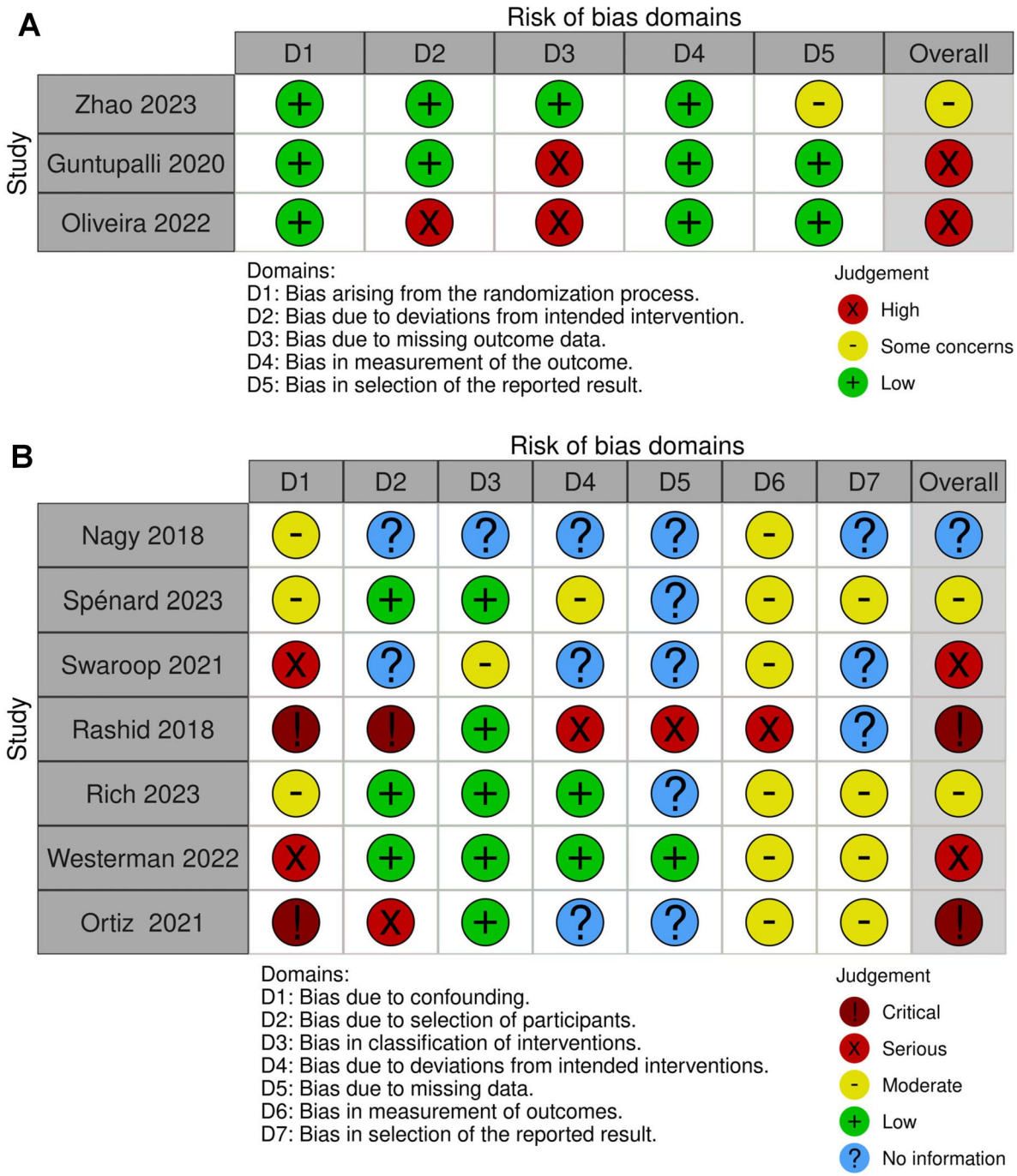

Fig. 2 Risk of bias assessment. **A** Risk of bias for randomized controlled trials, **B** Risk of bias for observational studies

analysis method that controlled for the confounding domain (Fig. 2B). Most observational studies had a bias of missing data [33, 34, 36–39]; however, one study that used a modified intention-to-treat analysis for compliance was adjudicated to a low risk of bias due to missing data [39] (Fig. 2B).Risk-of-bias plots were created by the tool [40].

Efficacy and safety outcomes

Primary efficacy outcome

Of the 10 studies, 30-day clinical VTE was assessed in 8 studies (3 RCTs [21, 22, 32] and 5 observational studies [34, 36–39]). We pooled the outcome by 30 days postoperative comparisons between DOAC and LMWH. During the 30-day postoperative period, DOACs (36/1019)

had a comparable incidence of VTE when compared to LMWH (62/1338) (3.5% vs. 4.6%, RR:0.69[95% CI:0.46–1.02], *P* value for Cochran Q = 0.92, $I^2 = 0\%$; Fig. 3A). Meanwhile, we also pooled the data from 4 studies (1 RCT [20] and 3 observational studies [32, 33, 37]) and showed no significant difference between both groups for postoperative VTE within 90 days (Supplementary Fig. 1A).

Primary safety outcome

30-day major bleeding was reported in 8 studies (3 RCTs [21, 22, 32] and 5 observational studies [34, 36–39]). There was no statistically significant difference in the incidence of major bleeding with DOAC (24/1019) compared with LMWH (18/1338) (2.4% vs. 1.3%, RR: 1.55 [95% CI: 0.82–2.93], Cochran Q = 0.4, $I^2 = 2\%$; Fig. 3B). The result of 90-day major bleeding pooled data from 3 studies (1 RCT [20] and 2 observational studies [34, 37]) were consistent with those above (Supplementary Fig. 1B). CRNMB was reported in 5 studies (3 RCTs [21, 22, 32] and 2 observational studies [34, 39]). DOACs had a comparable risk of CRNMB when compared to LMWH (3.4% vs. 4.2%, RR, 0.89 [95% CI, 0.4–1.98], *P* value for Cochran Q = 0.22, $I^2 = 31\%$; Fig. 3C).

Subgroup analysis

We conducted a subgroup analysis of 30-day VTE and major bleeding according to the study type (RCTs versus observational studies), duration of thromboprophylaxis (extended versus non-extended), tumor type (gynecologic malignancy, urological malignancy, and lung cancer), and different types of DOAC. The results showed no significant differences and were summarized in Supplementary Fig. 2A–4B. In addition, sensitivity analyses were conducted to show no significant influence on the results of sequential removal of each study (Supplementary Table 2).

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis to directly compare the effectiveness and safety of DOACs and LMWH for thromboprophylaxis in postoperative patients by combining RCTs and observational studies. In this systematic review and meta-analysis, DOACs and LMWH for thromboprophylaxis seemed to have similar efficacy and safety profiles in terms of subsequent venous thromboembolism and clinically relevant bleeding complications. The results did not seem to differ between RCTs and observational studies, extended thromboprophylaxis, or tumor type.

The degree of VTE risk in patients undergoing cancer surgery varies according to the type and duration of surgery, immobilization status of the patient and the presence of other VTE risks in the cancer surgery patient [4]. In our meta-analysis, there was a low 30-day postoperative rate of VTE between the DOAC and LMWH groups (3.5% vs. 4.6%), which is similar to that previously reported in other cancer-related surgery trials [21, 22]. One RCT of lung cancer with non-extended prophylaxis included in the studies showed a higher incidence of VTE and MB than other studies of abdominopelvic cancer with extended prophylaxis. However, subgroup analysis suggested no difference according to the duration of thromboprophylaxis (extended or non-extended) and tumor type (gynecologic malignancy, urological malignancy, and lung cancer). Lung cancer is associated with a higher risk of VTE than other malignant solid organ tumors [41, 42]. Extended thromboprophylaxis reduced the tenfold risk of pulmonary embolism in patients who underwent resection of primary lung cancer and was independently associated with a reduction in postoperative PE [43]. Therefore, DOACs might be an efficacious alternative to LMWH for extended thromboprophylaxis to reduce risk of VTE in patients undergoing lung cancer resection surgery, and further studies are warranted.

Regarding the safety of major bleeding and CRNMB, no statistical significance was found in our meta-analysis. Previous studies have shown that patients with gastrointestinal cancer have a high rate of major hemorrhage [44, 45]. However, updated meta-analyses of randomized trials found that major bleeding occurred more frequently with DOACs, but there was no difference in the risk of overall major bleeding between DOACs and LMWH for cancer-related venous thromboembolism [46–48].

The results of the present study should be interpreted with caution because of the following limitations. First, the number of three RCTs in the meta-analysis was small, and seven of the ten included studies were observational studies, which may have introduced bias. However, the subgroup analysis suggested no differences between RCTs and observational studies, and the outcomes of observational studies were consistent with those of RCTs. Second, the types of medications used were mainly apixaban and rivaroxaban. Future studies are encouraged to investigate other DOACs used in VTE prophylaxis in cancer-related surgery. Therefore, we used a subgroup analysis to reduce the impact of these potential limitations. Thirdly, although the long-term effect of DOAC versus LMWH in postoperative thromboprophylaxis is consistent with the 30-day effect, there are few included studies and more RCTs of long-term effects are needed. Lastly, the tumor type was mainly gynecologic malignancy and urological malignancy, and additional evidence is expected for gastrointestinal malignancies and other malignant tumors.

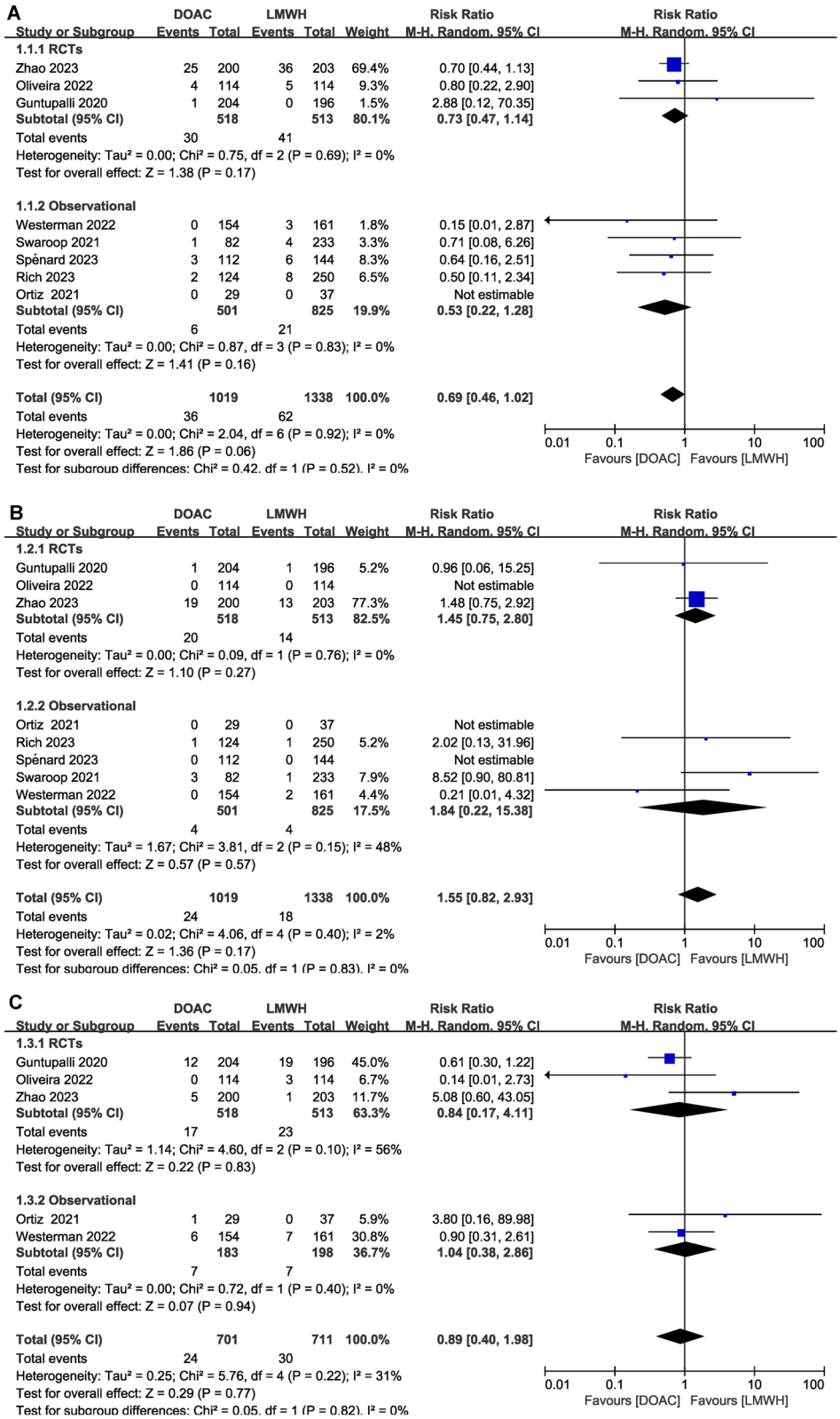

Fig. 3 Forest plots of relative risks (RRs) for pooled outcome by 30 days postoperative comparisons between DOAC and LMWH, stratified by study design. **A** VTE, **B** Major bleeding, **C** Clinically relevant non-major bleeding (CRNMB)

Conclusion

DOACs are equivalent to LMWH in preventing postoperative VTE as thromboprophylaxis after cancer-related surgery. These findings suggest that oral DOACs (apixaban and rivaroxaban) are potentially effective and safe alternatives to subcutaneous LMWH for thromboprophylaxis in patients undergoing cancer surgery. Further studies are needed for thromboprophylaxis in patients with gastrointestinal malignancies and other tumors undergoing surgery.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12957-024-03341-5.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

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Authors' contributions

H.Z., T.-T.C contributed to the conception of the study, literature review, and manuscript preparation; H.Z. and T.-T. C and L.-L.Y. contributed significantly to data acquisition; J.-J.M. and J.-H.Z. helped perform the analysis with constructive discussions.

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Availability of data and materials

This is a meta-analysis article, and data availability is not applicable. Please contact the corresponding author if data are needed.

Declarations

Ethics approval and consent to participate

This meta-analysis has no ethical approval.

Competing interests

The authors declare no competing interests.

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