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Prophylactic direct oral anticoagulants vs. low molecular weight heparin after urological surgery: A systematic review and meta-analysis

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ABSTRACT

Purpose: To compare the outcomes of using prophylactic direct oral anti-coagulants (DOAC) and low-molecular-weight heparin (LMWH) after major urologic surgery.

Materials and Methods: Systematic literature searches of MEDLINE, Embase, Web of Science, and Cochrane CENTRAL were performed up to 9 November 2023, and protocols were registered on PROSPERO (CRD42024494424). The primary outcomes were post-operative incidence of VTE and bleeding. The secondary outcomes included re-admissions and transfusions needed, post-operative complications and exploring the radical cystectomy sub-group. Outcomes were reported in 30 and 90 days where feasible with sub-group analysis.

Results: Searches yielded four studies that included 856 patients and the outcomes were reported within 30 and 90 days, with sub-analysis performed for each time-interval. We found no statistically significant differences between DOAC and LWMH within neither primary nor secondary outcomes; VTE events (RR 0.36; $p = 0.06$); bleeding events (RR 0.64; $p = 0.45$); re-admissions (RR 1.14; $p = 0.39$); transfusions (RR 0.42; $p = 0.05$) within 0–90 days and post-operative complications within 30 days (RR 0.76; $p = 0.17$). Similar results were found when exploring radical cystectomy sub-group: VTE risk (RR 0.42, $p = 0.15$), bleeding risk (RR 1.09; $p = 0.90$), and re-admissions to hospital (RR 1.18, $p = 0.35$). Limitations include small sample size, and difficult generalization to all urological surgery as most of the analyzed cohort underwent radical cystectomy.

Conclusion: DOACs may be a safe and possibly cost-effective alternative to LMWH as post-operative thromboprophylaxis. However, these findings should be interpreted with caution due to limitations; therefore, more randomized studies are needed to ascertain our findings.

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Urology; venous thromboembolism; low-molecular-weight heparin; direct oral anticoagulant; surgery; radical cystectomy

Introduction

Venous thromboembolism (VTE) which includes deep vein thrombosis (DVT) and pulmonary embolism (PE) is a source of increased morbidity and mortality following major urological surgery [1–4]. A steady decline in the incidence of VTE has been demonstrated since the introduction of post-operative VTE prophylaxis protocols, with LMWH commonly used as the standard choice [1,5]. The introduction of direct oral anticoagulants (DOACs) has expanded anticoagulant options [6]. In the surgical context, the American Society of Clinical Oncology (ASCO) recently updated their guidelines with DOACs as an option for post-operative prophylaxis following oncological surgery [7]. A meta-analysis comparing DOACs to LMWH in non-cardiac surgeries illustrated the possibility of DOACs being an alternative to LMWH in post-operative thromboprophylaxis [8]. As LMWH is commonly administered via subcutaneous injection, fear of needles may present a barrier to adherence, whereas DOACs provide a convenient oral alternative. DOACs could improve patient adherence and possibly compliance [9]. Additionally, DOACs come with the added benefit of possible cost-effectiveness, as LMWH prescriptions tend to be more costly in some healthcare systems [9]. It is therefore worth investigating DOACs as an alternative to LMWH for post-operative thromboprophylaxis in urological surgery.

The primary aim of this systematic review and meta-analysis is to compare DOAC to LMWH in terms of incidence of post-operative VTE and post-operative bleeding at 30 and 90 days after urological surgery. The secondary aims are to compare post-operative complications in both groups at 30 and 90 days and to explore the same outcomes in the radical cystectomy sub-group.

Materials and methods

This systematic review and meta-analysis was performed in line with recommendations from the

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Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines and registered on PROSPERO (CRD42024494424).

Eligibility criteria

Inclusion in this systematic review and meta-analysis was restricted to studies that met all the following inclusion criteria. The article must compare DOACs to LMWH specifically, as prophylaxis against VTE. The patient population must have undergone major urological surgery. Some, or all relevant outcomes, such as the incidence of VTE, or bleeding events, must be reported by the study. Both randomized and non-randomized studies were permitted for inclusion, with no restrictions regarding time of patient follow-up. Articles that satisfied any of the following exclusion criteria, however, were removed. Any anti-coagulation different to DOAC or LMWH, or a lack of head-to-head comparison between DOAC and LMWH, prompts exclusion. Populations that underwent surgery outside the field of urology were excluded. If no relevant outcome was reported, the study was excluded. Lastly, publications that were not observational cohort studies, such as review articles, case reports, and case series, were excluded.

Literature search

We searched the following databases: PubMed, Embase, Cochrane Library, and Web of Science. The search was conducted from inception up until 9 November 2023 and utilized the following terms as well as synonyms and relevant medical subheadings:

(1) 'Thrombus', 'Thromboembolism', or 'pulmonary embolism' and similar synonyms of thromboembolic disease.
(2) 'Direct Oral Anticoagulants' and synonyms as well as individual drugs such as 'rivaroxaban' or 'apixaban'.
(3) 'Low-molecular-weight heparin' and synonyms as well as individual drugs such as 'enoxaparin' were used.
(4) Urological surgeries such as 'cystectomy' and 'prostatectomy' as well as the medical subheading of 'urology'. We combined the four parts of our search strategy with the Boolean operator 'AND' and then used the Boolean operator 'OR' to cover synonyms within each sub-topic to maximize the breadth of our search strategy.

Two authors (M.R. and A.M.) independently screened extracted relevant articles following our predefined search criteria and quality assessment, which was completed on November 17, 2023. After retrieving studies from our primary databases, we implemented backwards and forwards snowballing, looking at which articles cite or were cited by the authors to help find more studies outside our databases. We also searched Google Scholar and searched for any previous systematic or narrative reviews for the inclusion of any grey literature such as conference/meeting abstracts, of which we failed to retrieve any.

Outcomes, endpoints, and sub-group analysis

Our primary outcomes of interest include any venous thromboembolic event reported, as well as bleeding events. VTE events include pulmonary embolism or deep vein thrombosis, and the incidence of such events within study cohorts constitutes our measurement of efficacy. Bleeding events are defined as any bleeding that prompts a visit to a hospital, and such an adverse event entails our main measurement of safety. Secondary outcomes include complications post-operatively, any blood transfusions needed, and re-admissions to hospital within 90 days.

We conducted sub-group analysis based on the time interval when the outcome was reported, e.g. bleeding risk at 30 days, and at 90 days. We also planned to conduct a separate sub-group analysis on radical cystectomy alone as our preliminary searches yielded data specific to radical cystectomy.

Quality assessment and risk of bias

We evaluated the risk of bias in randomized studies using version 2 of the Cochrane risk of bias assessment tool (ROB2) [10]. Non-randomized studies were assessed with the Risk of bias in non-randomized studies – of interventions tool (ROBINS-I) [11], and we used the GRADE assessment to present a summary of evidence and our judgement.

Two independent authors completed quality of studies assessment (M.R. and J.H.). Disagreements were resolved through a consensus after discussion of reasons for discrepancy.

Publication bias assessment was investigated by funnel-plot analysis of point estimates in relation to study weights.

Statistical analysis

Risk-ratios (RR) with 95% confidence intervals were used to compare treatment effects for categorical endpoints. Continuous outcomes were compared with standardized mean differences. A p value < 0.05 was considered statistically significant. We assessed heterogeneity with i^2 statistics and Cochran Q test; p-values <0.10 and I2 $>25\%$ were considered significant for heterogeneity

We used DerSimonian and Laird random-effects model for plots with substantial heterogeneity (>25%) and a fixed effect model for plots with low heterogeneity (<25%). We also performed two sensitivity analysis: (1) removing each individual study from the outcome assessment and (2) using adjusted risk estimates from non-randomized studies, when available. Review manager 5.4 (Cochrane center, the Cochrane collaboration, Denmark) was used for statistical analysis.

Results

Study selection and baseline characteristics

As detailed in Figure 1, the initial search yielded 2138 results, with 15 studies remaining after removal of duplicate and ineligible records. A total of four studies comprising 856 patients were included after fully reviewing articles, all of which were non-randomized comparative observational studies, three implemented retrospectively, and one implemented prospectively.

Study characteristics

Table 1 describes patient baseline characteristics. In four studies comprising 856 patients, 353 patients received DOAC (41%), and 503 patients (59%) received LMWH as post-operative VTE prophylaxis. Most patients across all studies underwent radical cystectomy (76%; $n = 652/856$), although one study included various other urological oncological surgeries such as prostatectomy and nephrectomy. In their LMWH cohort, Rich et al. [12] administer unfractionated heparin or enoxaparin post-operatively throughout the patient's admission, until discharge, and then administer 40 mg subcutaneous enoxaparin daily for 21 days. The DOAC group received apixaban 2.5 mg

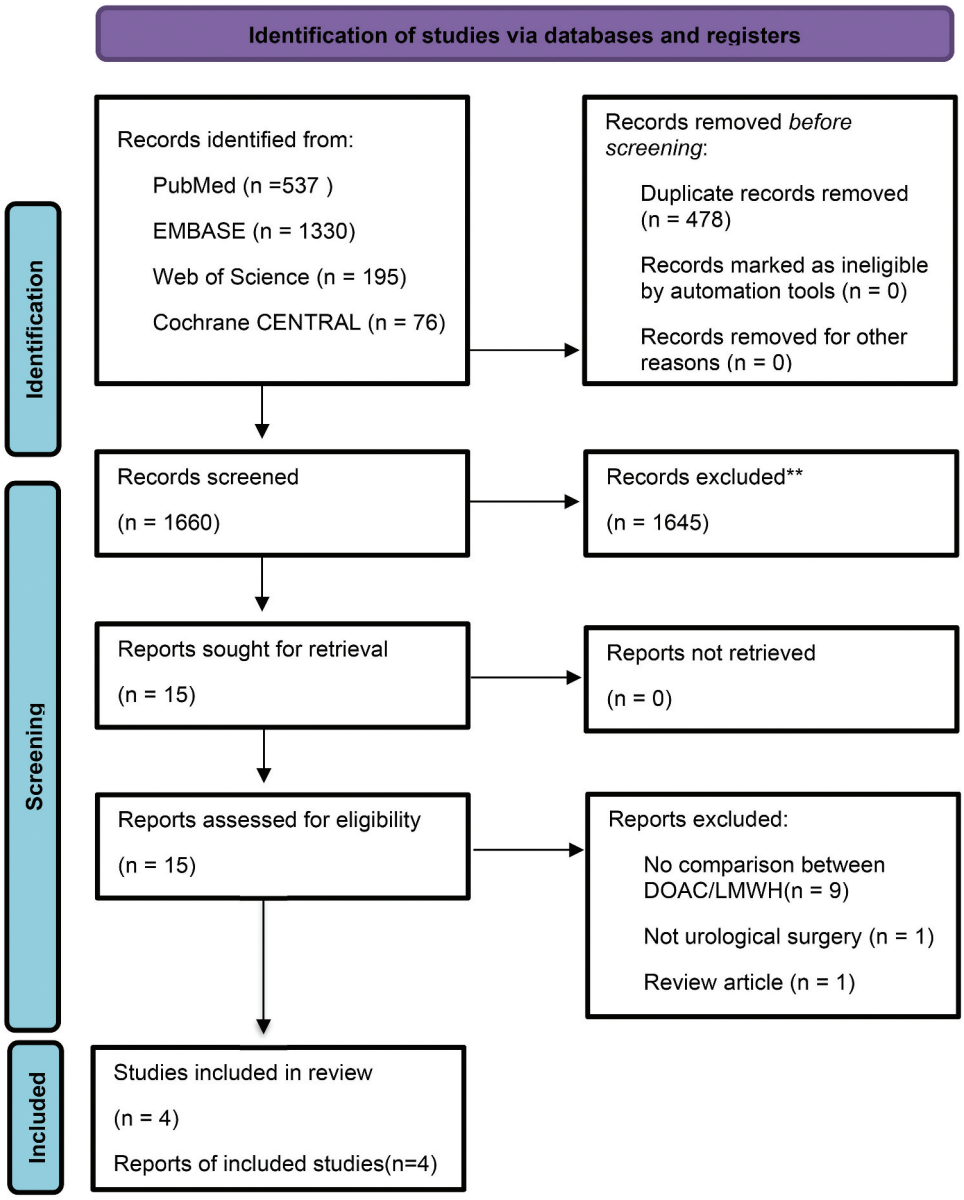

Figure 1. PRISMA flow diagram for study screening.

Table 1. Baseline characteristics of included studies.

Median Follow-up (LMWH/ DOAC)	Outcome(s)	Control drug of choice (no. of patients)	Intervention (no. of patients)	History of VTE (LMWH/ DOAC)	No. of Diabetics (LMWH/ DOAC)	No. of Smokers (LMWH/ DOAC)	Sex M/F	BMI[†]	Age[†], y	Surgery Done	No. of patients (LMWH/ DOAC)	Design	Study
30–90 days	VTE, major bleeding, re-admissions, mortality	Enoxaparin (250)	Apixaban (124)	3/0	55/25	46/18	291/83	26.1 (22.9–29.7)	69 (63–76)	RARC	(250/124)	Non-RCT	Rich [12]
30–90 days	VTE, major bleeding, post op complications, readmission	Enoxaparin (37)	Rivaroxaban, apixaban, Dabigatran (29)	5/3	NA	8/5	46/20	27.8 (16.9–50.2)	67 (44–85)	RARC	(37/29)	Non-RCT	Ortiz [13]
30 days	VTE, major bleed and non-compliance events	Enoxaparin (161)	Apixaban (154)	NA	NA	NA	257/58	29.7 (26.2–35.0)	66 (58–73)	Oncologic al	(161/154)	Non-RCT	Westerman [14]
90 days	VTE and major bleed	Enoxaparin (55)	Rivaroxaban, Apixaban (46)	NA	6/7	6/7	69/32	27 (23.7–30.6)	71 (63–76)	Radical Cystectomy	(55/46)	Non-RCT	Faraj [15]

[†]Mean or median; RCT: DOAC: Direct Oral Anti-Coagulant; LMWH: Low Molecular weight heparin; Randomised control trial; RARC; Robotic assisted radical cystectomy.

twice daily, from post-operative day 1, throughout hospital admission, and 21 days after discharge as well. Ortiz et al. [13] also used enoxaparin 40 mg in 33/37 (89%) patients, but variable doses such as 60 mg twice daily were also used. Their DOAC group also used a variety of DOAC regiments, most of which received rivaroxaban 10 mg daily in 21/29 (72%) of patients, but also included daily 5 mg of apixaban in 3/29 (10%) of patients. Their prophylactic course lasted 30 days post-operatively, and DOAC was used after 5 days of LMWH. Westerman et al. [14] used 2.5 mg of apixaban twice daily, and 40 mg of enoxaparin daily, with prophylaxis lasting 28 days after discharge from hospital. Most of their patient cohort received no thromboprophylaxis post-operatively, up until discharge. Lastly, Faraj et al. [15] used either rivaroxaban 10 mg daily, or 2.5 mg of apixaban twice daily in their DOAC cohort, for 30 days, after 3 days of 5000 units of heparin given post-operatively. Their control group utilised 40 mg of enoxaparin daily. Variability was found between studies in terms of bleeding outcome criteria and time of follow-up.

Pooled analysis of studies

Primary outcomes

There was no statistically significant difference in between patients receiving DOAC or LMWH as thromboprophylaxis in terms of bleeding or VTE incidence. In Figure 2, no statistically significant difference between DOAC and LMWH was found in VTE events in 0–90 days (0.85% VS 3.18%; RR 0.36, 95% CI [0.12, 1.03]; ($p = 0.06$); $i^2 = 0\%$). There was also no statistically significant difference when analyzing sub-groups of 30, and 90-day outcomes of VTE events, respectively; ($p = 0.21$) and ($p = 0.15$). Heterogeneity was inapplicable for 30-day outcomes but was low in 90-day outcomes ($i^2 = 0\%$). Exclusionary sensitivity analysis demonstrated no significant differences when pulling individual studies out.

In Figure 3, no statistically significant difference was found in bleeding events between DOAC and LMWH (0.85% VS 1.39%; RR 0.64; 95% CI [0.2–2.03]; ($p = 0.45$); $i^2 = 0\%$) upon analysis with a fixed effect model. There was no statistically significant difference when analyzing bleeding sub-groups of 30 and 90 days, respectively; ($p = 0.36$) and ($p = 0.89$). Moderate heterogeneity was found in 30-day bleeding event risk ($i^2 = 40\%$; $p = 0.2$). Exclusionary sensitivity analysis demonstrated no significant differences when pulling individual studies out.

Secondary outcomes

In (Figure 4), no statistically significant difference was found between DOAC and LMWH in terms of readmissions in 0–90 days (18.41% VS 16.9% RR 1.14; 95% CI [0.85, 1.53]; ($p = 0.39$); $i^2 = 0\%$). There was also no statistically significant difference when analyzing subgroups of 30- and 90-day outcomes of readmissions, respectively; ($p = 0.79$) and ($p = 0.21$). Exclusionary sensitivity analysis demonstrated no significant differences when pulling individual studies out

In (Figure 5), no statistically significant difference between DOAC and LMWH was found in terms of transfusions needed in 0–90 days (3.5% VS 6.23%; RR 0.42; 95% CI [0.18, 0.98]; ($p = 0.05$); $I^2 = 0\%$). Minimal heterogeneity was found [$i^2 = 0\%$]. Using a random effects model, however, yielded ($p = 0.04$), which significantly favored DOAC.

In (Figure 6), no statistically significant difference between DOAC and LMWH was found in post-operative complications within 0–30 days (33% VS 46%; RR 0.76; 95% CI [0.51, 1.12]; ($p = 0.17$) i2 = 32%). Moderate heterogeneity was present ($i^2 = 32\%$; $p = 0.23$).

Outcomes in radical cystectomy

In Figure 7, no statistically significant difference was found between groups in terms of VTE incidence after radical cystectomy within 0–90 days (1.507% VS 3.801%; RR 0.42; 95% CI [0.13, 1.35] ($p = 0.15$) $i^2 = 0\%$). Minimal heterogeneity was found ($i^2 = 0\%$; $p = 0.91$). Exclusionary

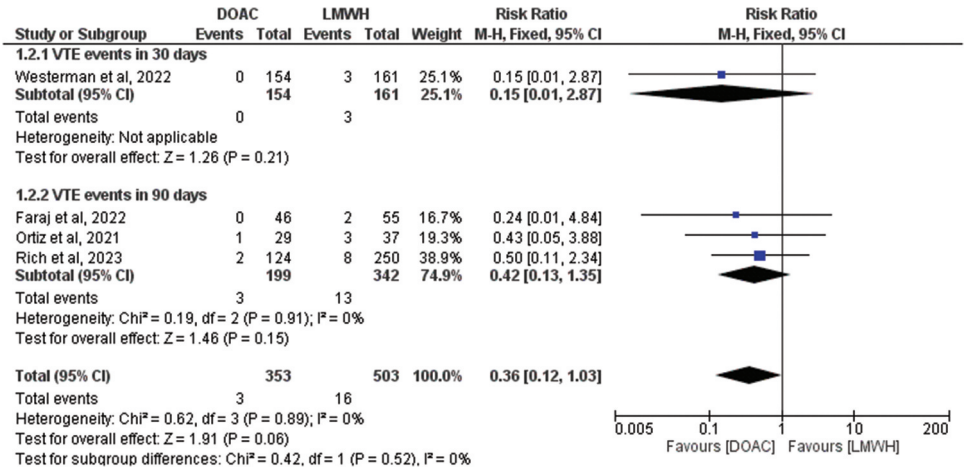

Figure 2. Forest plot assessing VTE events in up to 90 days.

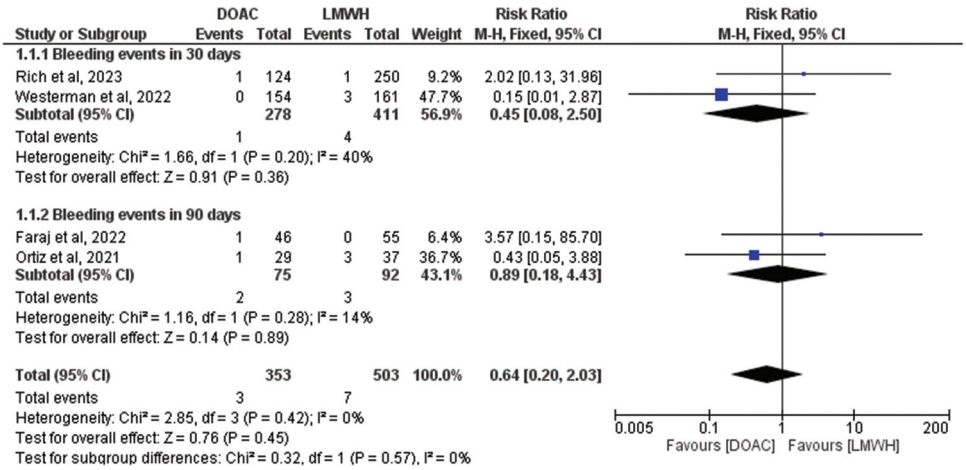

Figure 3. Forest plot analysing bleeding events in up to 90 days.

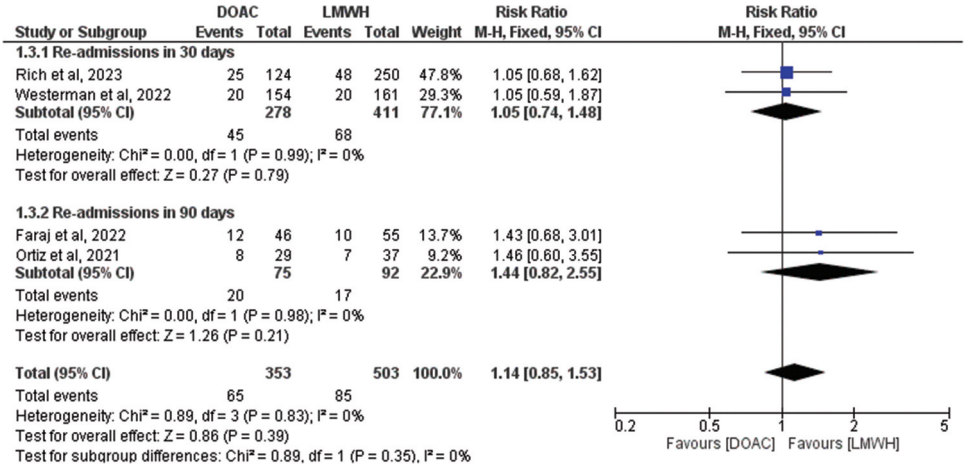

Figure 4. Forest plot analysing re-admissions to hospital in up to 90 days.

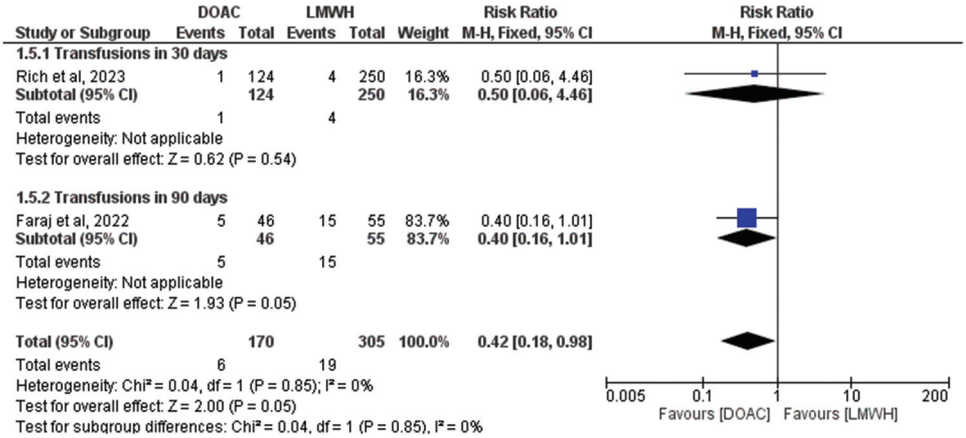

Figure 5. Forest plot analysing transfusions needed in up to 90 days via fixed effect model.

sensitivity analysis demonstrated no significant differences when pulling individual studies out.

In (Figure 8) no statistically significant difference was found between groups in terms of incidence of bleeding after radical cystectomy within 0–90 days (1.507% VS 1.169%; RR 1.09; 95% CI [0.24, 4.27] $p = 0.90$). Minimal heterogeneity was found ($i^2 = 0\%$, $p = 0.49$). Exclusionary sensitivity analysis demonstrated no significant differences when pulling individual studies out.

In (Figure 1, supporting material), no statistically significant difference was found between groups in re-admissions to hospital in 90 days after radical cystectomy (22% VS 19%; RR 1.18 95% CI [0.84, 1.66] $p = 0.35$). Minimal heterogeneity was found ($i^2 = 0\%$)

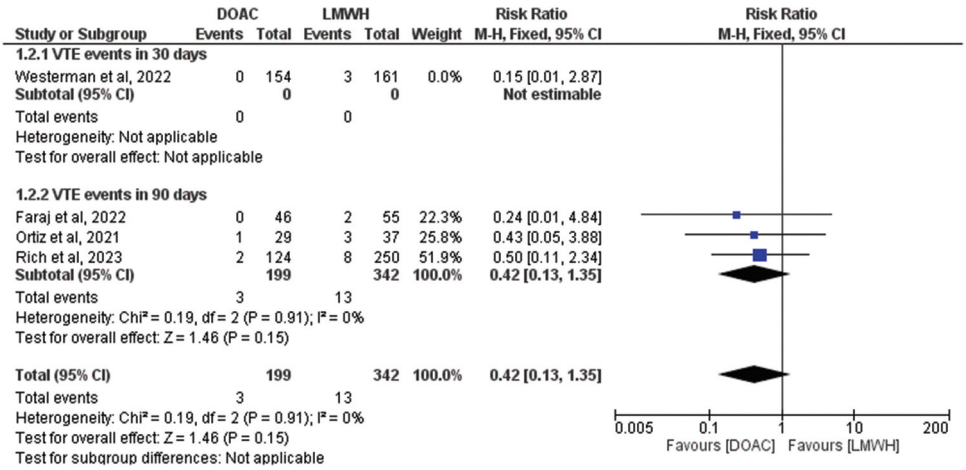

Figure 6. Forest plot analysing post-operative complications in 30 days.

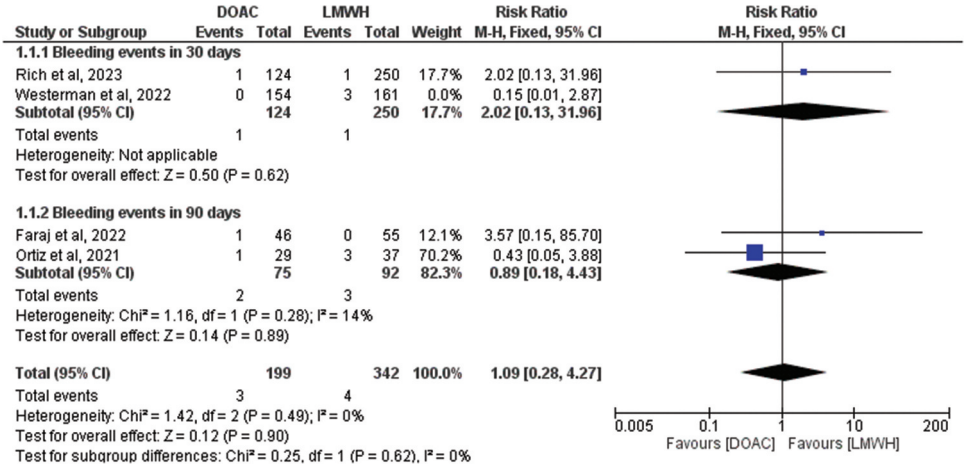

Figure 7. Forest plot analyzing VTE events in 0–90 days in radical cystectomy patients.

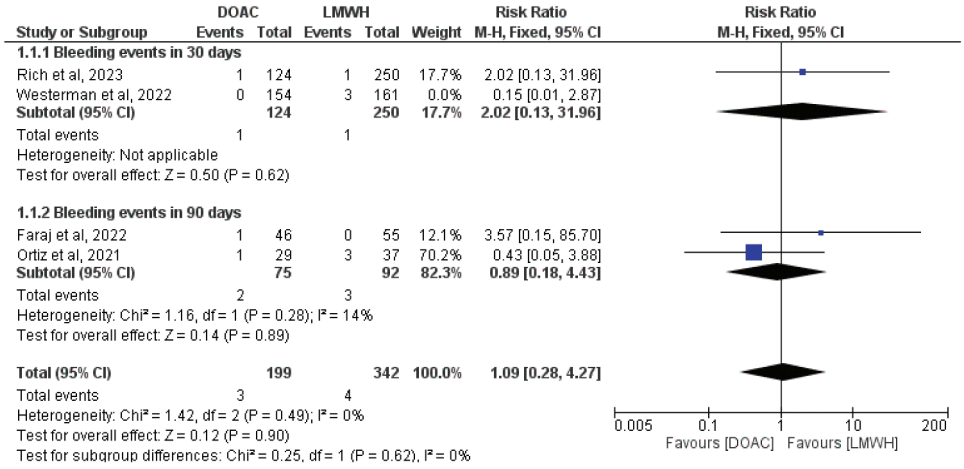

Figure 8. Forest plot analysing bleeding events in 0–90 days in radical cystectomy alone.

Quality assessment of studies and risk of bias

The Risk of Bias in Non-randomised Studies tool by Cochrane (ROBINS-I) was used to assess the quality of studies and risk of bias, as detailed in Figure 9. Two studies carried a potential serious risk of bias upon assessment, and two studies carried a potential moderate risk of bias. No studies were deemed low risk for bias.

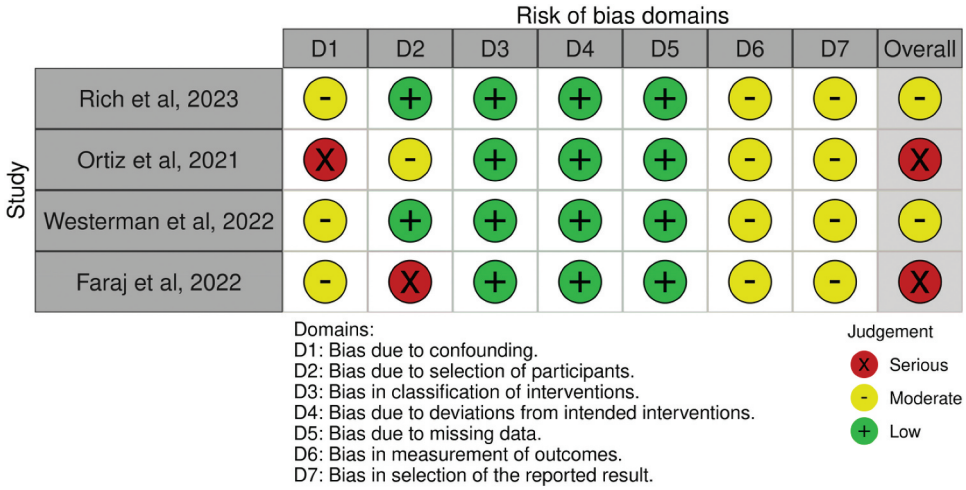

Figure 9. Risk of bias assessment using ROBINS-I.

On funnel plot analysis for publication bias of primary outcomes, studies occupied asymmetrical distribution regarding VTE events (Figure 2, supporting material). However, studies occupied a symmetrical distribution via funnel plot, regarding the primary outcome of bleeding events (Figure 3 supporting material) according to weight, and converged towards the pooled effect as weight increased.

On funnel plot analysis of secondary outcomes, studies occupied symmetrical distribution according to weight, and converged towards the pooled effect as weight increased, regarding the outcomes of readmissions in 90 days, and post-operative complications in 0–30 days (Figures 4 and 5, supporting material). However, studies occupied an asymmetrical distribution via funnel plot when analyzing the outcome of transfusions in 0–90 days (Figure 6, supporting material).

We summarize our findings using the GRADE assessment in Figure 10.

DOAC compared to LMWH for Urological Surgical Post-operative Thromboprophylaxis

Patient or population: Urological Surgical Post-operative Thromboprophylaxis
Setting: Hospital
Intervention: DOAC
Comparison: LMWH

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with LMWH	Risk difference with DOAC
Bleeding events in 0-90 days	856 (4 non-randomised studies)	⨁⨁◯◯ Low[a,b]	**RR 0.73** (0.19 to 2.80)	14 per 1,000	**4 fewer per 1,000** (11 fewer to 25 more)
VTE events in 0-90 days	856 (4 non-randomised studies)	⨁◯◯◯ Very low[a,b,c]	**RR 0.37** (0.13 to 1.10)	32 per 1,000	**20 fewer per 1,000** (28 fewer to 3 more)
Re-admissions in 0-90 days	856 (4 non-randomised studies)	⨁⨁◯◯ Low[a,c,d]	**RR 1.14** (0.85 to 1.54)	169 per 1,000	**24 more per 1,000** (25 fewer to 91 more)
Post-operative complications in 0-30 days	440 (2 non-randomised studies)	⨁◯◯◯ Very low[e,f,g]	**RR 0.76** (0.51 to 1.12)	460 per 1,000	**110 fewer per 1,000** (225 fewer to 55 more)
Transfusions in 0-90 days	475 (2 non-randomised studies)	⨁◯◯◯ Very low[c,e,g]	**RR 0.41** (0.18 to 0.97)	62 per 1,000	**37 fewer per 1,000** (51 fewer to 2 fewer)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. 2/4 studies contained a potential serious risk of bias
b. RR <0.75, wide confidence interval
c. Asymmetry on funnel plot analysis, however small quantity of studies may render funnel plot insufficient to draw conclusions from
d. Re-admissions may be secondary to a wide variety of variables giving rise to confounding and weakening the direct nature of this outcome to our clinical question
e. 1/2 studies contained a potential serious risk of bias
f. Heterogeneity i2 = >30%, likely due to a low number of studies and small sample size
g. RR < 0.75; wide confidence interval with very low number of studies producing potential bias

Figure 10. Summary of Findings Table using the GRADE assessment.

Discussion

In this systematic review and meta-analysis, we found no statistically significant differences between DOAC and LMWH at 90 days in terms of VTE ($p = 0.06$), bleeding risk ($p = 0.45$), readmissions ($p = 0.39$), transfusions required ($p = 0.05$), and lastly post-operative complications at 30 days ($p = 0.17$). Sub-group analysis did not show differences in the outcomes at 30 or 90 days or outcomes in the radical cystectomy sub-group.

Our results are in keeping with findings in the published literature. Dabigatran was shown to be safe after prostatectomy in 398 patients, of which only one developed a VTE and nine developed bleeding [16]. Apixaban was also found to be safe, and effective in a cohort of 72 patients undergoing radical cystectomy, with no VTE nor bleeding experienced [17]. While these studies demonstrated safety in the urological setting, conclusions could not be drawn as no comparisons were made to the standard LMWH. Furthermore, several meta-analyses demonstrated the safety and efficacy of DOACs in comparison to LMWH injections post-operatively, although most of the evidence is reported within orthopedic surgery [8,18]. Marcucci and colleagues, however, demonstrated the safety and non-inferiority of DOACs in intra-abdominal surgery, but only included one study in urological surgery [8].

Radical cystectomy brings a particular population that has higher morbidity and VTE incidence compared to the remainder of urologic oncology surgery [19–21]. VTE occurrence is roughly 4–5%, expected within the first 20 days [19,20]. In an exploratory sub-group analysis, we analyzed 652 patients who underwent radical cystectomy found in the analyzed studies; DOACs were comparable to LMWH in preventing VTE up to 90 days ($p = 0.15$). There were no significant differences in terms of bleeding events ($p = 0.90$) or hospital re-admissions in up to 90 days ($p = 0.35$).

Current standard practice among urologists shows preference towards using LMWH as the standard thromboprophylaxis with only a minority opting for DOAC [5]. DOACs provide the convenience of an oral option compared to subcutaneous administration of LMWH. Patients may have several potential barriers with subcutaneous injections such as fear of needles, lack of healthcare professionals administering them, or inability to self-inject, which may impact compliance. Westerman and colleagues evaluated compliance in their cohort and noted better adherence with DOACs [14]. This was echoed by Khorana and colleagues, where they found improved continuity of treatment with DOAC compared to LMWH, as well as a tendency of patients switching from LMWH to other anticoagulants [22]. On the other hand, Schaefer and colleagues found no significant differences between DOAC (95.6% adherence) and LMWH (94.6% adherence) [9]. Despite the conflicting data assessing compliance, treatment should ideally be individualized to the needs of the patients. If DOACs provide a safe and possibly equivalent alternative to LMWH, it ultimately serves the individual patient to have that choice.

Furthermore, data from Spain and the United States suggest higher prescription costs associated with LMWH compared to DOAC [9,23]. Schafer notes an average cost of 153.61$ for LMWH vs 40.67$ for DOAC, while Munoz and colleagues note a 12-month cost of 1994€ for DOAC, and 2152€ for LMWH. Bhalla et al.'s cost-analysis suggests savings of $39 per patient per day by using apixaban compared to enoxaparin, and they also estimated a higher non-adherence rate in LMWH (23% non-adherence) compared to DOAC (10% non-adherence) [24]. This is further echoed by Li et al., estimating 5-year savings of 24,129$ when using DOAC instead of LMWH [25]. Such cost savings are beneficial to the healthcare system, and become more imperative when factoring in the cost burden of VTE on hospitals [26].

That being said, what is the appropriate regiment for patients? Our studies mostly incorporated apixaban, however, both rivaroxaban, and dabigatran were also utilized. The doses and duration of prophylaxis also varied, although prophylaxis generally lasted 21–30 days. Apixaban 2.5 mg, twice daily, was most commonly used. As most of our cohort went radical cystectomy, apixaban may therefore be a more suitable option, compared to rivaroxaban, which may carry a higher risk of bleeding according to literature studying CKD, and CVD patients [27,28]. A challenge also arises as DOACs are cleared by the kidney [29], carrying important implications to urological patients whom may already present with impaired renal function, or are due for nephrectomy. Dabigatran in particular has a clearance of up to 80% in the kidney, which could make it less favorable [29]. This discussion remains a hypothesis, as there was a paucity of direct comparison between DOACs for surgical patients under urology, to the best of our knowledge. Therefore, a significant gap in the literature needs to be filled with robust research, to elucidate an ideal regiment for patients.

Our findings suggest that DOACs are a possible safe and effective alternative to LMWH for patients undergoing urological surgery. We believe this is an attractive option for patients and urologists, and it is less costly for healthcare systems. These hypothesis generating findings should be explored in a prospective fashion as it may expand the standard of care options.

Strengths and limitations

To the best of our knowledge, this is the first meta-analysis to investigate this topic. Additionally, we further

explored the radical cystectomy cohorts within the studies, which represents the highest risk sub-group for VTE and complications and is the group of most interest in the field. However, limitations must be taken into account when interpreting our findings. Firstly, we have a limited sample of 4 studies and 856 individuals and none of the included studies are randomized, which places them at a significant risk of bias. Even though patients needed less transfusions in 90 days when on DOAC is noteworthy, analysis of this outcome only included two studies, one of which had a serious risk of bias, weakening our certainty. There was also variability in follow-up and reporting outcomes within 30 and 90 days. While sub-analysis and a pooled analysis of data were performed, we cannot exclude that our sub-analysis was underpowered to detect any difference in outcomes. Substantial variability was also noted in the definition of bleeding within studies. Therefore, we cannot exclude that some studies may have under-reported bleeding outcomes due to more strict definitions of bleeding. Significant heterogeneity was noted in two of our outcomes (30-day complications and transfusions within 90 days). We hypothesize that this is likely due to the low number of studies. The vast majority of the cohorts included underwent radical cystectomy. It is therefore difficult to generalize our findings to all urological surgeries. Lastly, choosing the right prophylactic regiment remains a grey area needing significant research, for which we cannot confidently suggest meaningful changes to guidelines, as of yet.

Conclusions

In this meta-analysis, we were able to demonstrate that there is no difference in VTE and bleeding outcomes between DOAC and LMWH in major urologic oncology surgeries. These findings could potentially support future use of DOAC as a safe and cost-effective alternative to LMWH. However, our findings are with limitations, which render generalizations difficult. Further studies are needed to validate our findings.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Author contributions

All authors contributed to the study conception and design. All authors contributed to drafting of the manuscript. All authors commented on previous versions of the manuscript, then read and approved the final manuscript. Preparation of materials was done by Mohammed Ramadhan, Abdullah AlMehandi, and Ahmad Almarzouq

Literature search was done by Mohammed Ramadhan

Screening of literature and study selection/acquisition was done by Mohammed Ramadhan, and Abdullah AlMehandi

Data extraction was done by Mohammed Ramadhan and Jafar Hayat

Statistical analysis was done by Mohammed Ramadhan and Abdulrahman Al-Naseem

Quality assessment and risk of bias were done by Mohammed Ramadhan and Jafar Hayat

Interpretation of data and results was performed by Mohammed Ramadhan, Abdulrahman Al-Naseem, and Ahmad Almarzouq

Supervision of the project and senior critical review was provided by Ahmad Almarzouq

Abbreviation list

DOAC	Direct Oral Anticoagulants
LMWH	Low Molecular Weight Heparin
VTE	Venous thromboembolism
DVT	Deep Venous Thrombosis
PE	Pulmonary Embolism
RARC	Robotic assisted radical cystectomy
RCT	Randomized Controlled Trials
RR	Risk Ratio

Data availability statement

All authors made sure that all data and materials as well as software application or custom code support their published claims and comply with field standards. The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Use of AI

No AI nor AI-assisted technology was used in scientific writing of this manuscript by any of the authors.

There was no involvement of any animal, nor human subjects in this research, and due to the nature of this review article, no ethical nor institutional review was sought, nor required.

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