

Use of direct oral anticoagulants for postoperative venous thromboembolism prophylaxis after surgery for gynecologic malignancies

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ABSTRACT

Venous thromboembolism is a preventable cause of postoperative mortality in patients undergoing surgery for malignancy. Current standard of care based on international guideline recommends 28 days of extended thromboprophylaxis after major abdominal and pelvic surgery for malignancies with unfractionated heparin or low molecular weight heparin. Direct oral anticoagulants have been approved for the treatment of venous thromboembolism in the general population. This regimen has a significant advantage over other types of anticoagulation regimens, particularly being administered by non-parenteral routes and without the need for laboratory monitoring. In this review, we evaluate the role of direct anticoagulation and provide an update on completed and ongoing clinical trials.

INTRODUCTION

Direct oral anticoagulants are now standard treatment for cancer associated thromboembolisms. Their safety and efficacy have been proven in multiple randomized controlled trials in the past 5 years.^{1–3} The role of direct oral anticoagulants as prophylaxis for venous thromboembolism after abdominal and pelvic surgery for gynecology malignancies has not been well established. It is well known that following surgery for malignancy, the risk of venous thromboembolism is doubled compared with patients undergoing non-cancer surgery.^{1,2,4} A recent study by Li et al highlighted that in patients undergoing surgery for ovarian, fallopian tube, or peritoneal cancer, implementation of an enhanced recovery after surgery protocol, which includes 28 days of thromboprophylaxis with low molecular weight heparin, reduced the risk of venous thromboembolism in the first 30 days to 2.2% from a previously reported risk of 7.5%.^{4,5} It has also been shown that venous thromboembolism acquired after surgery for malignancy was associated with reduced overall survival time, particularly for ovarian cancer.^{4–6} The @RISTOS project is an observational study reporting the incidence of overt venous thromboembolism in patients with cancer after surgery. The incidence of venous thromboembolism was 2.83% in general surgery, 2.0% in gynecologic

surgeries, and 0.87% in urologic surgery.⁷ Most importantly, 46% of deaths reported were found to be associated with venous thromboembolism.⁷ It is a preventable cause of postoperative mortality.^{1–4}

In gynecologic cancers, ovarian cancer patients are 1.5 times more likely to have a venous thromboembolism compared with other gynecologic cancers (ovarian cancer 3% (95% confidence interval (CI) 1.10 to 2.16) vs uterine cancer 2.4% vs cervical cancer 1.5%, and vulvar cancer 1.2%).^{8,9} The current recommendation from international guidelines is for 4 weeks of extended thromboprophylaxis after major abdominal and pelvic surgery for malignancies with unfractionated heparin or low molecular weight heparin.^{1,10} Apart from a recent updated statement published by the Society of Gynecologic Oncology, there are currently no formal recommendations for use of direct oral anticoagulants in this prophylactic setting.¹

Direct oral anticoagulants have a significant advantage over low molecular weight heparin as they are taken orally rather than administered parenterally, without the need for laboratory monitoring.^{11,12} A significant barrier to compliance with postoperative venous thromboembolism prophylaxis is the need for daily, sometimes twice daily, subcutaneous injections with low molecular weight heparin or unfractionated heparin.¹¹ It is therefore unsurprising that the COSIMO (Cancer associated thrombosis—patient reported outcomes with rivaroxaban) study, a prospective cohort study recruiting 500 patients with active cancer receiving low molecular weight heparin then switching to rivaroxaban, a type of direct oral anticoagulant, found higher patient treatment satisfaction and treatment persistence with rivaroxaban compared with low molecular weight heparin.¹²

The aim of this narrative review is to describe the types of direct oral anticoagulants currently available in the clinical setting, with particular focus on apixaban and rivaroxaban, and present the most recently completed and ongoing studies investigating the safety and efficacy of direct oral anticoagulants for use as venous thromboembolism prophylaxis after gynecologic oncology surgery. The safety of direct

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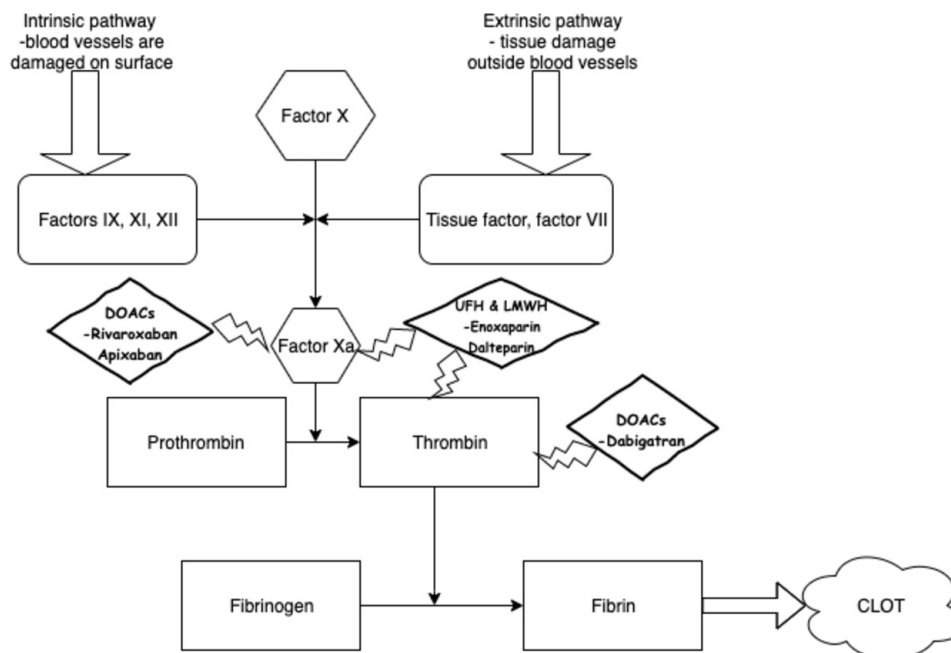


Figure 1 Coagulation cascade, depicting the site of action of various anticoagulation therapies. DOACs, direct oral anticoagulants; LMWH, low molecular weight heparin; UFH, unfractionated heparin.

oral anticoagulants is assessed by the rate of major bleeding after such surgery, while efficacy is measured by incidence of venous thromboembolism.

Search Strategy

A comprehensive electronic search of PubMed, Medline, Scopus, and Google Scholar was performed to identify eligible studies. The search was limited to the last 10 years (2011–2021) and English language. Key words for the literature search included (“gynaecolog* cancer*” OR “gynecolog* cancer”) AND (“direct oral anti coagulation” OR direct oral anticoagulants * OR rivaroxaban OR apixaban) AND (“venous thrombo*” OR “venous thromboembolism” OR “thrombo*”) AND (prophylaxis OR prevention).

OVERVIEW OF DIRECT ORAL ANTICOAGULANTS PHARMACOLOGY

Currently, there are two classes of direct oral anticoagulants: (1) direct thrombin inhibitor (dabigatran) and (2) direct factor Xa inhibitors (rivaroxaban, edoxaban, and apixaban).^{13 14} Dabigatran irreversibly binds to thrombin, preventing the breakdown of fibrinogen to fibrin in the coagulation cascade, stopping the development of a thrombus. The second group of direct factor Xa inhibitors act earlier in the clotting cascade by preventing the conversion of prothrombin to thrombin, also inhibiting the formation of fibrin^{13 14} (Figure 1).

The onset of the anticoagulation effect for all direct oral anticoagulants is relatively rapid, with peak plasma levels reached within 1–4 hours.^{13 14} The half-lives of rivaroxaban, apixaban, and dabigatran are 9–13 hours, 8–15 hours, and 14–17 hours, respectively.^{13 14} Compared with other anticoagulations, such as vitamin K antagonists (warfarin), direct oral anticoagulants have a more predictable pharmacokinetics and anticoagulant response.^{13 14} The rates of renal excretion for rivaroxaban and apixaban are 60% and 25%, respectively. Given the predominant renal elimination

rate of rivaroxaban, it is contraindicated in patients with a creatinine clearance of <15 mL/min.^{13 14} On the other hand, apixaban is mainly excreted via the fecal route which could be more suitable for patients with impaired kidney function.^{13 14}

DIRECT ORAL ANTICOAGULANTS: GUIDELINES FOR POSTOPERATIVE THROMBOEMBOLISM PROPHYLAXIS

The initial data describing the safety and efficacy of direct oral anticoagulants for postoperative venous thromboembolism prophylaxis originated from orthopedic surgery.¹⁵ When administered 12–24 hours after surgery at either 2.5 mg twice daily of apixaban or 10 mg daily of rivaroxaban, both were superior to low molecular weight heparin (enoxaparin) at reducing the risk of symptomatic venous thromboembolism postoperatively (pooled odds ratio (OR) 0.46, 95% CI 0.3 to 0.7), without increasing the risk of bleeding.¹⁵

Until recently, data for the use of direct oral anticoagulants in venous thromboembolism prophylaxis following abdominal and pelvic surgery for malignancy were not available. Because of this lack of evidence, multiple treatment guideline groups have yet to recommend its use in this setting. CHEST 2016, American Society of Clinical Oncology, National Comprehensive Cancer Network, and the European Society of Medical Oncology have all recommended that pharmacologic thromboprophylaxis following surgery for malignancy should currently be unfractionated heparin for up to 4 weeks.^{10 11 16–18} Following favorable results from a non-inferiority trial by Guntupalli et al, the Society of Gynecologic Oncology has recently updated their practice statement to include the use of apixaban as pharmacologic prophylaxis for venous thromboembolism in patients undergoing laparotomy for gynecologic malignancies for up to 4 weeks.¹⁹

DIRECT ORAL ANTICOAGULANTS AFTER GYNECOLOGIC ONCOLOGY SURGERY

At present, there is only one completed randomized controlled trial assessing the use of direct oral anticoagulants in patients following surgery for gynecologic malignancy. Guntupalli et al enrolled 400 women with suspected or known gynecologic malignancies undergoing surgery¹⁹ (online supplemental Table 1). Approximately half of their study population were randomized to 2.5 mg of oral apixaban twice a day and other half to 40 mg subcutaneous low molecular weight heparin (enoxaparin).¹⁹ Both medications were administered for 28 days. The primary outcome assessed the safety of apixaban prophylaxis compared with low molecular weight heparin. The authors found no significant difference between the groups in terms of major bleeding events, with only one event in each group (OR 1.04, 95% CI 0.07 to 16.76).¹⁹ There was also no difference in clinically relevant non-major bleeding events, such as hematoma, bruising, vaginal bleeding, or epistaxis (OR 1.88, 95% CI 0.87 to 4.1). Additionally, to assess efficacy, there was no difference in venous thromboembolism events between groups: 1% in the apixaban arm and 1.5% in the low molecular weight heparin arm (OR 0.63, 95% CI 0.12 to 3.75).¹⁹ The study was, however, underpowered to detect a significant difference in bleeding risk between the groups as bleeding events were much lower than anticipated (0.5% per group rather than 2% difference as anticipated). The authors concluded that this result would suggest that apixaban is safe to use for postoperative thromboprophylaxis following gynecologic oncology surgery but a larger non-inferiority randomized trial is required to demonstrate a true difference.¹⁹

In the study of Guntupalli et al, the efficacy of apixaban was demonstrated by the similar venous thromboembolism outcomes in both groups (apixaban 1.0% vs enoxaparin 1.5%). In fact, the incidence of venous thromboembolism was much lower in both groups than previously demonstrated in the literature, likely owing to high adherence rates because of the clinical trial setting.¹⁹ Although the efficacy data from this study are promising, the study was not designed to assess the efficacy of apixaban as venous thromboembolism prophylaxis. Patients in the apixaban group reported a significantly higher satisfaction rate than the enoxaparin group, particularly with ease of use (98.9 vs 58.8%).¹⁹

Until the study by Guntupalli et al, the use of direct oral anticoagulants in the postoperative venous thromboembolism prophylaxis setting had not been evaluated. This study showed promising data, suggesting the safety and efficacy of apixaban following surgery. Until more data emerge, the use of direct oral anticoagulants postoperatively should be individualized, taking into account the patient's comorbidities, bleeding risk and preference.

Swaroop et al performed a retrospective study of 315 women who received either enoxaparin or oral rivaroxaban for postoperative extended thromboprophylaxis after laparotomy for the treatment of gynecologic malignancy.²⁰ The primary outcome evaluating the incidence of venous thromboembolism in the enoxaparin group at 30 days was 1.7% versus 1.2% in the rivaroxaban group ($p=1.0$).²⁰ No significant difference was seen in the rate of major bleeding events between the enoxaparin group (0.4%, 1/233) compared with rivaroxaban (3.7%, 3/82).²⁰ These findings should be interpreted cautiously given the retrospective nature of this study as well as the small sample size. Nevertheless, it showed that rivaroxaban may be

safe and effective in the postoperative thromboprophylaxis setting, paving the way for larger prospective studies.

To introduce direct oral anticoagulants as an alternative standard of care in the role of venous thromboembolism prophylaxis after gynecologic oncology surgery, efficacy data are vital. The VALERIA study (NCT04999176) is a multicenter randomized controlled trial evaluating the efficacy and safety of oral rivaroxaban versus enoxaparin for venous thromboembolism prophylaxis after major gynecologic cancer surgery.²¹ This randomized controlled trial is the first in the literature designed to assess the efficacy of rivaroxaban in venous thromboembolism prevention. The VALERIA study started recruiting in October 2020 and the expected completion date is July 2024.²¹

SAFETY OF DIRECT ORAL ANTICOAGULANTS

It has only been in the past 5 years, since the availability of cancer specific data, where direct oral anticoagulants have become the preferred anticoagulation treatment for cancer associated thromboembolisms (in a non-operative setting). The initial concern of increased bleeding risk with direct oral anticoagulant use in this population has since been alleviated by large studies.^{1 10}

A meta-analysis by Li et al in 2019 included studies comparing the safety and efficacy of direct oral anticoagulants with low molecular weight heparin in the treatment of venous thromboembolism in patients with malignancy. This study showed that while direct oral anticoagulants were effective at reducing the risk of recurrent venous thromboembolism, the risk of major bleeding (relative risk (RR) 1.74, 95% CI 1.05 to 2.88) and non-major bleeding was higher (RR 2.31, 95% CI 0.85 to 6.28).² The two randomized controlled trials that Li et al analyzed were the Hokusai CANCER study comparing edoxaban with dalteparin, and the SELECT-D study comparing rivaroxaban with dalteparin.^{22 23} A similar but updated meta-analysis by Giustozzi et al included the Hokusai CANCER and SELECT -D studies, as well as the ADAM-venous thromboembolism and the more recent Caravaggio study.²⁴⁻²⁶ Both the ADAM-venous thromboembolism and the Caravaggio study compared the safety and efficacy of apixaban versus dalteparin in the treatment of cancer associated thromboembolisms. Unlike the Li et al study, when apixaban was added to the analysis of edoxaban and rivaroxaban, the risk of major bleeding in the direct oral anticoagulants population was not significantly different compared with dalteparin (RR 1.31, 95% CI 0.83 to 2.08).^{2 25} This study also found that direct oral anticoagulants were superior in reducing the risk of recurrence compared with dalteparin (RR 0.62 95% CI 0.43 to 0.91).²⁵

A Ukrainian retrospective cohort study by Tyselskyi et al evaluated the safety of 10 mg rivaroxaban taken once a day following major colorectal surgery for 30 days.²⁷ In this study, 41.2% of surgeries were laparotomies while 58.8% were laparoscopic surgeries.²⁷ A pre-existing malignancy was the indication for 90% of these surgeries. By day 3 after surgery, all patients were transitioned from postoperative low molecular weight heparin to rivaroxaban, once they were able to tolerate a regular diet and were hemoglobin stable.²⁷ Three of 51 patients developed bleeding complications; 1 of these 3 patients returned to the operating theater.²⁷ There were no venous thromboembolisms recorded within 30 days.²⁷ The result from this study supported the safety and efficacy of

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rivaroxaban but was limited by the study's retrospective nature and small population.

Orthopedic studies have demonstrated the safety of apixaban and rivaroxaban used postoperatively.¹⁵ In the setting of venous thromboembolism prophylaxis postsurgery for malignancy, there are no meta-analyses at present due to the lack of randomized controlled trials. As reviewed previously, the only published randomized controlled trial by Guntupalli et al showed promising apixaban safety compared with enoxaparin.¹⁹

EXTENDED THROMBOEMBOLISM PROPHYLAXIS AFTER MINIMALLY INVASIVE SURGERY FOR GYNECOLOGIC MALIGNANCY

The advantages of minimally invasive surgery in most oncologic settings are well known. Patients generally mobilize earlier as a consequence of shorter hospital stays and less pain, minimizing the risk of venous thromboembolism.^{28 29} This should be weighed against factors associated with minimally invasive surgery that increase the risk of venous thromboembolism, such as reverse Trendelenburg position, pneumoperitoneum, and potentially longer operating time.²⁹ There is no current consensus on the use of extended venous thromboembolism prophylaxis following minimally invasive surgery for malignancy.

A recent retrospective cohort study of 806 patients with gynecologic cancer found that the incidence of venous thromboembolism after 90 days following minimally invasive surgery was 0.6%.³⁰ In this study, 97% received immediate postoperative unfractionated heparin prophylaxis and no patients received extended venous thromboembolism prophylaxis after discharge.³⁰ The authors concluded that extended venous thromboembolism prophylaxis is not 'supported' in patients undergoing minimally invasive surgery for gynecologic cancers.³⁰ However, their cohort was predominantly white with an average body mass index of 34 kg/m².

In a similar study, Graul et al found that patients with gynecologic cancers undergoing minimally invasive surgery were 66% less likely to develop a venous thromboembolism (OR 0.34, $P < 0.0001$) compared with those undergoing open procedures.⁹ This study also showed that patients with advanced stage in the minimally invasive surgery group were 5.96 times more likely to have a venous thromboembolism regardless of the primary site of the gynecologic malignancy.¹⁰ Unfortunately, a limitation of the study was the lack of information regarding the types of venous thromboembolism prophylaxis used in their cohort. However, it does highlight the importance of risk stratification as the risk of venous thromboembolism cannot be considered similar for all minimally invasive surgeries.

The advantage of extended venous thromboembolism prophylaxis was demonstrated in a study of 301 patients undergoing minimally invasive surgery for colorectal cancer randomized to either short (1 week) or extended (4 weeks) duration low molecular weight heparin. The incidence of venous thromboembolism was 9.7% in the short duration group versus 0.9% in extended duration group ($p = 0.005$).²⁸

At present, international guidelines, such as the American Society of Clinical Oncology and the European Society of Medical Oncology, do not distinguish between surgical modalities in the use

of extended venous thromboembolism prophylaxis after surgery for malignancy.^{10 18} This is because current research does not specifically address minimally invasive surgery and mainly includes data from open surgeries. In the context of direct oral anticoagulant use, the only randomized controlled trial previously described by Guntupalli et al included 20% minimally invasive surgery and 80% open surgery, and primary or secondary outcomes were not analyzed by surgical modalities.¹⁹ Given the limited evidence, the Society of Gynecologic Oncology has recommended that the decision for use of direct oral anticoagulants following minimally invasive surgery for malignancy be individualized based on risk factors for venous thromboembolism.¹

DIRECT ORAL ANTICOAGULANTS: COST CONSIDERATIONS

The absolute event numbers for postoperative venous thromboembolism for malignancy may be small but the negative impact it has on patient morbidity and mortality is significant. Additionally, venous thromboembolism treatment has a large economic burden on healthcare systems.^{4 6 31-33} Cost effectiveness for extended thromboprophylaxis with low molecular weight heparin following major oncological abdominal surgery was assessed by Iannuzzi et al.³¹ Using a decision analytic model, they compared cost and health outcomes of inpatient 7 day thromboprophylaxis versus 28 days, both using low molecular weight heparin. The authors concluded that following surgery for malignancy, when venous thromboembolism probability exceeded 0.88%, extended thromboprophylaxis is cost effective.³¹ This would apply to patients undergoing surgery for gynecologic malignancy based on the @RISTOS project.⁷ A systematic review and meta-analysis by Serrano et al demonstrated that the incidence of venous thromboembolism in patients undergoing abdominal and pelvic surgery for cancer without use of postoperative thromboprophylaxis can remain elevated 3 months after surgery. The authors described a rate of up to 9.6% in prospective cohort studies (including colorectal, gynecology, and hepatobiliary malignancies) and up to 1.2% in subgroup analyses in patients undergoing gynecologic oncology surgery.³⁴ Similar results were highlighted in a more recent Canadian study aimed to determine the cost effectiveness of extended thromboprophylaxis with low molecular weight heparin in patients after colorectal surgery for malignancy.³² In that study, extended prophylaxis was associated with a higher cost but overall an increased quality adjusted life years (+0.05, 95% CI 0.04 to 0.06) reflecting an incremental cost effectiveness ratio of USD\$2473/quality adjusted life year.³²

A cost effective analysis by Glickman et al compared 28 days of apixaban with enoxaparin in the prevention of venous thromboembolism following gynecologic oncology surgery.³³ The authors found that overall, apixaban had a lower aggregated net cost compared with enoxaparin (apixaban USD\$175 967 vs enoxaparin USD\$202,981).³³ By disaggregated results, apixaban was superior in cost effectiveness in the prevention of deep vein thrombosis events (net savings of \$258,995) but not cost effective in the prevention of pulmonary embolism. This might be due to lower reported deep vein thrombosis rates compared with pulmonary embolism rates although individual venous thromboembolism outcomes are difficult to analyze as clinical trials would often report composite venous thromboembolism outcomes. Interestingly, the

event cost per patient which incorporates inpatient, outpatient, and pharmaceutical treatments was estimated at USD\$20 397 for deep vein thrombosis and USD\$22 144 for pulmonary embolism.³³ The authors also concluded that these data could be extrapolated to patients undergoing surgery for non-gynecologic cancers.

DIRECT ORAL ANTICOAGULANTS: PRECAUTIONS

Metabolism of direct oral anticoagulants may be difficult to predict in patients undergoing cancer surgery due to a wide variety of reasons.^{1 6} Nausea and vomiting are common side effects of major abdominal and pelvic surgery. This may affect the absorption and compliance of direct oral anticoagulants. In this situation, it may be preferable to consider low molecular weight heparin initially. Procedures where the gastrointestinal anatomy is altered may affect the bioavailability of direct oral anticoagulants.^{1 35} Since apixaban is predominantly absorbed in the proximal small bowel, any resection of this segment of bowel will affect its bioavailability.^{13 14 35} Usually its bioavailability is 50–80%.^{13 14} Rivaroxaban is predominantly absorbed in the stomach; its bioavailability is usually 80% when taken with food.^{13 14} Any gastric resection for malignancy will directly affect the bioavailability of rivaroxaban.^{1 34 36}

Thrombocytopenia may occur following neoadjuvant chemotherapy or due to a secondary immune mediated response. Patients with thrombocytopenia, particularly if the platelet count is $<50 \times 10^9/L$, should avoid direct oral anticoagulants due to the increased risk of bleeding.^{1 16 35} Medications that inhibit cytochrome P450, such as ketoconazole, and CYP 3A4 inducers, such as rifampicin, carbamazepine, and phenytoin, as well as P-glycoprotein inhibitors and inducers, such as itraconazole, erythromycin, azithromycin, or clarithromycin, can affect the plasma concentrations of direct oral anticoagulants impacting safety and efficacy.^{1 16 35} Patients on these medications should be recommended low molecular weight heparin for postoperative venous thromboembolism prophylaxis instead of direct oral anticoagulants.

CONCLUSION

The use of direct oral anticoagulants as venous thromboembolism prophylaxis following abdominal and pelvic surgery for malignancy is an emerging practice that could improve treatment compliance and therefore optimize postoperative outcomes. Current evidence suggests promising data for the safety and effectiveness of direct oral anticoagulants, specifically apixaban. There is currently only one randomized controlled trial in the setting of gynecologic malignancy. In the absence of further large prospective randomized trials, current use of direct oral anticoagulants as extended venous thromboembolism prophylaxis in the clinical setting is not considered a standard recommendation; however, this regimen could be individualized according to the patient's risk of venous thromboembolism and bleeding.

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