

# Direct Oral Anti-Coagulants Continue to Bud into Gynecological Cancer-Thrombosis Prevention

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“Everyone is not your costumer”. -Seth Godin

Some cancer-surgeries are best poised to lead a change in thromboprophylaxis.

Gynecological cancers (GYN-ONC) have been grouped to equate a high thrombosis risk,<sup>1,2</sup> this welcomes the strong interest on implementing effective strategies to reduce the burden of cancer-associated thrombosis. Indeed, there is general agreement by major societies that 4 weeks of post-surgical thromboprophylaxis is the standard of care in gynecology-oncology.<sup>3</sup> Yet not everyone is my costumer, understanding the heterogeneous rates if venous thromboembolism (VTE) after GYN-ONC surgery and comparing the efficacy of anticoagulants beyond low molecular weigh heparin will mark the pace in the evolution of thromboprophylaxis. VALERIA (Venous thromboembolism prophylaxis after gynecoLogical pELvic cancer surgery with RIvaroxaban vs enoxAparin) in this version of The Journal, is moving the dial.

Using mandatory ultrasound, in the VALERIA trial the authors found 4 events in the (3.5%) of 114 patients assigned to post operative rivaroxaban 10 mg PO and 5 events (4.4%) among the 114 patients assigned to SC enoxaparin 40 mg for 30 days. The composite safety outcome of major bleed or clinically relevant non major bleed was low with no events in the rivaroxaban group (0%) and 3 in the enoxaparin arm (2.6%). The results are encouraging in suggesting rivaroxaban as an alternative to enoxaparin in GYN-ONC prophylaxis, yet the trial was stopped early, and these results are exploratory. The reported rates are comparable those described at 90 days in a retrospective comparison of by Swaroop et al which also compared enoxaparin (4.3%) to rivaroxaban (2.4%) after GYN-ONC surgery.<sup>4</sup> Partially explained by the screening ultrasound, the rates of VTE are sobering, nonetheless that our best practice still found 1 in 25 patients to have VTE perioperatively. It is generally accepted that incidentally found thrombotic events herald morbidity in patients with cancer. As we expand on thromboprophylaxis alternatives, shall we also re-learn the lessons of risk stratification? Against this background, in a 63 000-patient

report by the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) the 30-day incidence of VTE in GYN-ONC surgery dropped from 1.7% to 0.9% in the last decade. The incidence is higher in patients with ovarian (2.4%) and uterine cancer (2.4%) relative to those with cervical cancer (1.1%). Thus, assigning high risk tier to all GYN-ONC may be oversimplified. Currently, no predictive strategy is validated to target preventive tactics to the patients with highest risk, yet this group includes those with low albumin, disseminated cancer, ascites, longer or high complexity surgery.<sup>5</sup> The Caprini risk score is widely used in perioperative VTE risk prediction, thus, in a cohort of 1123 GYN-ONC surgical patients the use of the Caprini score predicted patients at the highest risk thrombosis.<sup>6,7</sup> In VALERIA, less than half the patients were reported to have a high Caprini score, it remains to be described if a risk-based thrombosis prevention strategy is effective using DOAC in GYN-ONC.

VALERIA joins another recent 400 women trial among patients who needed GYN-ONC surgery; in which apixaban (1%) and enoxaparin (1.5%) groups also had similar VTE rates (OR, 1.6; 95%CI, 0.3–9.5;  $P = .7$ ). Patients received the intervention drug for 4 weeks; on the apixaban arm received 2.5 mg BID and those on enoxaparin received 40 mg SC daily with no difference on major bleeding rates (0.5% on both arms).<sup>8</sup> Although promising, the trial was tempered by design as it did not plan to define efficacy. Also exploring direct oral anticoagulant efficacy in oncologic surgery, the PROphylaxis of venous thromboembolism

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after LAParoscopic Surgery for colorectal cancer Study II (PROLAPS II) study compared rivaroxaban (10 mg daily 3 weeks) or a placebo started  $7 \pm 2$  days and the composite rate of confirmed VTE (symptomatic or asymptomatic by ultrasound), or VTE related death was lower in the rivaroxaban arm 3.9% versus 1.0%; OR 0.3; 95%CI, 0.1–0.9) with no excess in major bleeding.<sup>9</sup>

While the literature is still not conclusive on absolute efficacy, there is a definite paradigm shift occurring. Indeed, the Society of Gynecologic Oncology has issued a Clinical Practice Statement based on this data that includes the use of DOACs as an acceptable alternative for VTE treatment and prophylaxis for patients with gynecologic cancer.<sup>10</sup> As evidence accumulates to consider DOACs a safe and likely effective alternative after some oncologic surgeries, a patient-centered approach likely will add to adoption. Adherence to DOACs perioperatively and patient satisfaction are rated higher of oral anticoagulants compared to SC low molecular weight heparin.<sup>11</sup> When comparing apixaban to low molecular weight heparin for postoperative prophylaxis, patient satisfaction was significantly greater in the apixaban group with regard to ease of administration and pain associated with the medication which, aiming for a patient-centered practice, is highly desirable for a patient recovering from major surgery.<sup>8</sup>

Although DOACs are becoming increasingly desirable as evidence-based alternative in oncologic surgery thrombosis prevention, this task is still undone. Several questions remain unanswered in cancer-thrombosis surgical prophylaxis, as we must ask: Is there a group of higher risk patients who need a modified prophylaxis strategy? How much real-life adherence and patient satisfaction is enough to outweigh efficacy uncertainty? Is the separation of GYN-ONC surgery from other oncologic surgery going to facilitate adoption? As we find more alternatives of thromboprophylaxis to protect patients undergoing oncologic surgery, trialists will continue to navigate a balance between fragmentation to select highest risk patients and maintaining explainable results that lead to adoption in clinical practice.


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