Commentary on: Rivaroxaban for Venous Thromboembolism Prophylaxis in Abdominoplasty: A Multicenter Experience

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We appreciate the opportunity to review this article by Dr Hunstad and his colleagues. The authors report on observed rates of venous thromboembolism (VTE) and reoperative hematoma in a case series of 132 abdominoplasty patients who received chemoprophylaxis with rivaroxaban 10 mg daily beginning 12 hours after surgery and continuing for ≥7 days.

The oral direct inhibitors of factor Xa (FXa) are the newest class of anticoagulant drugs and have ever-expanding indications. Factor X can be activated (to FXa) via either the intrinsic or extrinsic clotting pathways. FXa promotes conversion of prothrombin to thrombin, resulting in clot formation. Enoxaparin accelerates the activity of antithrombin, which accelerates the rate of inactivation of FXa. Inactivation of FXa subsequently decreases thrombin generation. Fondaparinux, the effect of which is largely mediated through FXa inhibition (with some inhibition of Factor IXa), is also an effective anticoagulant. Clinical utility of fondaparinux identified FXa as an appealing target for anticoagulants because it represents a unifying pathway of the intrinsic and extrinsic clotting pathways.

Rivaroxaban is an oral direct inhibitor of FXa. Rivaroxaban is approved by the United States Food and Drug Administration for prevention of stroke and systemic embolism for patients with nonvalvular atrial fibrillation, treatment of acute VTE, long-term prevention of recurrent VTE after an initial 6 months of therapy, and prevention of VTE after total knee or hip arthroplasty. Approval was based on large phase III trials showing noninferior or superior efficacy and similar or reduced rates of major, intracranial, and fatal bleeding compared with conventional anticoagulants (ie, enoxaparin and/or warfarin). For patients undergoing total knee arthroplasty, rivaroxaban 10 mg daily reduced the primary outcome of VTE and death compared with enoxaparin 40 mg daily (9.6% vs 18.9%, P < .001) without increased bleeding. Similar findings were observed after total hip arthroplasty. Rivaroxaban also offers several practical advantages compared with conventional anticoagulants. It is taken orally, does not require routine laboratory monitoring, and has relatively few diet and drug interactions. Collectively, these attributes recommend rivaroxaban as a promising candidate for chemoprophylaxis after plastic and reconstructive surgery, albeit with a paucity of data at present.

Patient compliance and cost are 2 important considerations in chemoprophylaxis. A study in the United Kingdom showed that dalteparin, a low molecular weight heparin given by subcutaneous injection, was less expensive than dabigatran, an orally administered direct thrombin inhibitor, for VTE prophylaxis after lower extremity trauma. However, the overall costs with dalteparin were higher because several patients were unable to self-inject the medication and required home nursing for daily injections. Several studies have examined patients’ willingness and ability to self-administer injections. Seruya et al reported on 14 plastic surgery patients at high risk for postoperative VTE. Compliance with self-administered injectable prophylaxis was 93%. In other surgical populations, directed education sessions with a pharmacist or a registered nurse in the peri-operative period have been shown to improve medication compliance. The

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combination of inpatient teaching and availability of a registered nurse for phone consultation may decrease or eliminate the need for nurse medication administration after discharge, with some studies reporting 100% compliance.13 Teaching a friend or relative to administer the injections may also improve compliance.14

Calculation of a patient’s baseline VTE risk is an important preoperative consideration. The authors report risk stratification using the currently unvalidated Davison modification of the Caprini score.15 Of note, risk stratification for plastic surgery patients using the 2005 Caprini score16 has been formally recommended in the American Society of Plastic Surgeons17 and American Association of Plastic Surgeons (AAPS)18 consensus statements on VTE prophylaxis, based on extensive validation studies with over 17,000 patients. Existing validation studies include studies in patients who had plastic and reconstructive surgery (n = 1126),19 general, vascular, or urologic surgery (n = 8216),20 otolaryngology head and neck surgery (n = 2016),21 gynecologic oncology surgery (n = 1123),22 and patients in the surgical intensive care unit (n = 4844).23 Risk-factor modification is an important consideration in VTE risk reduction. The authors report their standard practice for VTE prevention, which includes perioperative intermittent pneumatic compression, early ambulation, knee flexion, and adequate hydration. These are all important nonpharmacologic methods to minimize VTE risk. We commend the authors as well for preoperative referral of patients with a personal or family history of VTE to hematology, as has been advocated by others.24 Hematologists are better prepared than plastic surgeons to evaluate patients for thrombophilia and make recommendations regarding appropriate VTE prophylaxis strategies.

While not a focus of this study, the authors note that all procedures were performed under general anesthesia. General anesthetic can eliminate the action of the calf muscle pump, which, in turn, promotes venous stasis. Venous stasis is a central tenet of Virchow’s Triad for thrombosis. Several large case series report low deep venous thrombosis (DVT) rates (or no DVT events) when anesthetic mechanisms that preserve the calf muscle pump are utilized.25-28 However, even SAFE (Spontaneous breathing, Avoid gas, Face up, Extremities mobile) anesthetic techniques, as advocated by Swanson and others, do not totally live up to their acronym. A recent report showed a 0.5% DVT rate when SAFE patients were critically evaluated with postoperative duplex ultrasound.29 A recent systematic review and meta-analysis sponsored by the AAPS made a GRADE 1C recommendation that “consideration should be given to using monitored anesthesia care, local anesthesia with sedation or neuraxial anesthesia instead of general anesthesia” for patients in whom nongeneral anesthetic was appropriate.18

The authors note that their average patient in the study had a 2005 Caprini score of 4. While the 2005 Caprini score has not been validated in the outpatient surgery population, the Plastic Surgery Foundation-sponsored Venous Thromboembolism Prevention Study (VTEPS) showed that 60-day VTE events among plastic surgery inpatients with Caprini scores of 3 to 4 were rare (0.3%-0.6%). Additionally, enoxaparin prophylaxis showed no benefit for VTE prophylaxis within this already low-risk group.30 The AAPS consensus panel showed that for the overall (eg, the non risk-stratified) plastic surgery population, there was no quantifiable benefit of routine chemoprophylaxis, but there was evidence of increased bleeding risk. The panel recommended against routine chemoprophylaxis for the overall plastic surgery population and instead recommended consideration of the risks and benefits of prophylaxis in a risk-stratified manner.18

This study by Hunstad et al is limited by lack of a comparison group. Thus, it cannot demonstrate whether rivaroxaban is superior or inferior to other means of mechanical or chemoprophylaxis. From the perspective of VTE rates, the study shows that 1 of 132 abdominoplasty patients (0.76%) who received postoperative rivaroxaban prophylaxis had a postoperative VTE event. From the perspective of VTE risk, this study provides us with additional evidence that VTE rates after abdominoplasty are generally low, especially when the procedure is performed among a low-risk group for VTE. In this study, the average 2005 Caprini score was 4. The observed VTE rate of 0.76% is similar to what has been published for other studies. A recent systematic review showed that the rate of VTE after abdominoplasty alone was 0.34% and after abdominoplasty with additional procedures was 0.67%.31 An analysis of over 7300 abdominoplasties in the Tracking Outcomes and Operations in Plastic Surgery (TOPS) database showed a DVT rate of 0.3% for abdominoplasty alone and 0.4% for abdominoplasty plus additional procedures.32

Three of 132 abdominoplasty patients (2.3%) had a reoperative hematoma after rivaroxaban prophylaxis was initiated. Of note, 2 patients (dropped from the analysis) had a reoperative hematoma within 12 hours after surgery; this was prior to their first dose of rivaroxaban. A prior analysis of over 7300 abdominoplasty patients in the TOPS database showed a hematoma rate of 0.9% for abdominoplasty alone and 1.0% for combined procedures.32 Given the small size of this study, and the lack of prophylaxis data in TOPS, it is impossible to compare the 2 studies. Postbariatric body contouring (but not chemoprophylaxis) was an independent predictor of reoperative hematoma in the VTEPS analysis of bleeding complications.33 Single-center studies have shown that bleeding rates are increased in surgeries with extensive areas of dissection and that this risk may further be increased when chemoprophylaxis is provided. It is noteworthy that this finding was not confirmed by the recent AAPS meta-analysis and consensus conference.18

This article provides important information specific to the oral FXa inhibitor rivaroxaban in abdominoplasty patients. One prior study by Dini et al was stopped due to an
unacceptably high rate of bleeding in abdominoplasty patients who received postoperative rivaroxaban.\textsuperscript{36} Specifically, 6 of 14 rivaroxaban patients and 0 of 13 placebo patients had a reoperative hematoma (G. Dini, personal email communication with AAPS consensus panel group, February 2015). The reason for the greater bleeding rates is not known. One possibility is that rivaroxaban was initiated 6 to 8 hours after surgery and patients were treated with concomitant nonsteroidal anti-inflammatory drugs (NSAIDs) in the Dini study whereas rivaroxaban was begun 12 hours after surgery in the Hunstad study and not routinely combined with an NSAID. Studies in other settings have confirmed that concomitant NSAID use is an independent risk factor for bleeding for patients on rivaroxaban.\textsuperscript{37} This study provides evidence that the bleeding risk in abdominoplasty patients who receive rivaroxaban prophylaxis may be acceptable if treatment is delayed until 12 hours after surgery and concomitant antiplatelet agents are avoided. Additionally, these data open the door for a comparative study to examine the relative risks and benefits of rivaroxaban and enoxaparin for VTE prevention. This study is underpowered to assess VTE risk reduction as a result of rivaroxaban prophylaxis, especially as the majority of patients were at low baseline risk for VTE events.

Routine chemoprophylaxis of lower-risk body contouring patients (eg, 2005 Caprini scores of 3-4) may not be necessary, and further data are needed to clarify when VTE chemoprophylaxis is appropriate among outpatients and patients classified as lower risk. The authors present enormously helpful data to further examine the safety profile of prophylactic dose rivaroxaban in abdominoplasty patients. We appreciate the opportunity to comment on their thought-provoking article and look forward to ongoing studies from their group.

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