

A review of traditional and novel oral anticoagulant and antiplatelet therapy for dermatologists and dermatologic surgeons

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Background: Dermatologic surgeons will increasingly encounter patients on novel oral antiplatelet and anticoagulant medications.

Objectives: We conducted a complete overview of the pharmacokinetics, pharmacodynamics, and side effects of traditional and novel oral anticoagulant and antiplatelet therapies along with dietary supplements with anticoagulant or antiplatelet properties.

Methods: A PubMed search was completed for “aspirin,” “warfarin,” “clopidogrel,” “dabigatran,” “rivaroxaban,” “apixaban,” “prasugrel,” and “ticagrelor.” Review articles and publications emphasizing perioperative management of oral anticoagulant or antiplatelet medications were selected. An additional PubMed search was completed for “hemorrhage,” “bleeding,” and “thrombosis” in conjunction with “dermatology,” “dermatologic surgery,” and “cutaneous surgery.”

Results: Aspirin, clopidogrel, and warfarin have shortfalls in dosing, monitoring, and efficacy. Several trials show superior efficacy with dabigatran, rivaroxaban, and apixaban, with equal or reduced risk of bleeding compared with warfarin. Prasugrel and ticagrelor may be associated with an increased bleeding risk. Many over-the-counter medications also have anticoagulant properties with associated bleeding risks that cannot be overlooked.

Limitations: There are few publications evaluating the novel oral anticoagulants’ effects on outpatient surgical procedures.

Conclusion: Novel anticoagulant and antiplatelet drugs are revolutionizing therapy for cardiovascular diseases. As these medications become more prevalent, dermatologists and dermatologic surgeons must be mindful of the bleeding risk that will apply in our everyday practices. (J Am Acad Dermatol 2015;72:524-34.)

Key words: anticoagulant; antiplatelet; apixaban; blood thinners; dabigatran; dermatologic surgery; dietary supplements; prasugrel; rivaroxaban; ticagrelor.

Cutaneous surgeries, both simple and complex, are considered safe procedures with a low risk of complications.¹ Although more complex dermatologic surgeries may have increased complications secondary to bleeding, it is expected that even these procedures would be unlikely to lead to life-threatening hemorrhagic complications.¹⁻⁶

Abbreviations used:

| | |
|---------|--------------------------------------|
| ADP: | adenosine diphosphate |
| AF: | atrial fibrillation |
| CVA: | cerebrovascular accident |
| FDA: | Food and Drug Administration |
| NSAIDs: | nonsteroidal anti-inflammatory drugs |

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However, dermatologic surgeons must be cognizant of the risks presented by individual patients. Because of age (average eighth decade) many dermatologic surgery patients have comorbidities requiring anticoagulation; approximately 46% of cutaneous surgery patients may take at least 1 anticoagulant or antiplatelet agent.¹⁻³ Bleeding risk associated with perioperative use of traditional anticoagulant or antiplatelet agents (warfarin, aspirin, and clopidogrel) has been previously reported¹⁻⁶; newer oral anticoagulant (dabigatran, rivaroxaban, and apixaban) and antiplatelet (prasugrel and ticagrelor) medications may pose similar risks to patients undergoing dermatologic surgery. In addition, over half of adults use over-the-counter products that may increase bleeding, and almost half of these patients do not report taking these supplements to their doctors.^{7,8}

ANTICOAGULANTS

Warfarin

With more than 33 million prescriptions written each year, warfarin is the most ubiquitous anticoagulant prescribed. Warfarin's indications and mechanism of action are listed in Table I and Fig 1.⁹⁻¹⁶ Numerous medications and supplements have potentially significant interactions with warfarin because of extensive protein binding and CYP2C9 metabolism (Table II).¹⁷

Bleeding is the major adverse event associated with warfarin, and risk of hemorrhage increases with the international normalized ratio, with a sharp increase once the international normalized ratio is above 4.5.^{16,18} Although some studies have shown a lack of bleeding complications during cutaneous surgeries in patients taking warfarin, a meta-analysis encompassing a total of 1373 dermatologic surgery patients found that those taking warfarin were nearly 7 times as likely to have moderate to severe bleeding-related complications (Table III) compared with control subjects.^{4,5,19} Furthermore, recent prospective studies have demonstrated a statistically significant increase in hemorrhagic complications in patients taking warfarin.¹

Certain patient characteristics have been identified in the Outpatient Bleeding Risk Index as validated risk factors for major spontaneous or perioperative bleeding events. These include age greater than 65 years, history of gastrointestinal bleeding, history of ischemic or hemorrhagic cerebrovascular accident (CVA), and presence of at least 1 of several comorbidities: myocardial infarction, hematocrit under 30%, creatinine above 1.5 mg/dL, diabetes, or a combination of these.¹⁸

Dabigatran

Dabigatran etexilate (Pradaxa, Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT), an oral direct thrombin inhibitor, was determined to be superior to warfarin for prevention of venous thromboembolism in patients with atrial fibrillation (AF) and equal or reduced bleeding risk.²⁰⁻²⁵ Dabigatran directly inhibits thrombin, preventing conversion of fibrinogen to fibrin (Fig 2). Although drug interactions are limited (Table II), dabigatran is a substrate of the efflux transporter P-

glycoprotein and is affected by inducers and inhibitors of this system.^{25,26} Prothrombin complex concentrate and recombinant factor VIIa have been proposed as reversal agents for dabigatran, but clinical studies are limited.²⁷ Thrombin time and ecarin clotting time have been evaluated as monitoring assays but are not currently routinely used to monitor drug efficacy.²⁸

The most common adverse effects of dabigatran are bleeding and gastrointestinal symptoms. Patients older than 75 years on dabigatran experienced a higher rate of bleeding when compared with warfarin; this increase was not noted in younger patients prescribed the same dose.^{22,23}

Rivaroxaban

Rivaroxaban (Xarelto, Janssen Ortho LLC, Gurabo, PR) was equivalent to warfarin for the prevention of thromboembolism in patients with high-risk AF and a reduced rate of fatal bleeding events. As a single agent, it has Food and Drug Administration (FDA) approval for CVA and

CAPSULE SUMMARY

- Although warfarin, aspirin, and clopidogrel are associated with increased hemorrhagic complications in dermatologic surgery, this risk is far outweighed by the risk of thrombosis when these medications are discontinued perioperatively.
- New oral anticoagulant and antiplatelet medications including dabigatran, rivaroxaban, apixaban, prasugrel, and ticagrelor carry a variable risk of bleeding.
- Until the specific risk associated with novel anticoagulant and antiplatelet medications in dermatologic surgery is established, these drugs should be managed similarly to traditional anticoagulants in the perioperative period.

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