

OPEN

# Perioperative Considerations for Antithrombotic Therapy in Oculofacial Surgery: A Review of Current Evidence and Practice Guidelines

Christian Kim, B.S., M.S.\*†, Margaret L. Pfeiffer, M.D.‡\*, Jessica R. Chang, M.D.‡, and Michael A. Burnstine, M.D.‡\*

\*Eyestetica, Los Angeles, California; †Department of Ophthalmology, Loyola University Stritch School of Medicine, Chicago, Illinois; and ‡USC Roski Eye Institute, University of Southern California Keck School of Medicine, Los Angeles, California, U.S.A.

**Purpose:** Recent survey studies have demonstrated wide variability in practice patterns regarding the management of antithrombotic medications in oculofacial plastic surgery. Current evidence and consensus guidelines are reviewed to guide perioperative management of antithrombotic medications.

**Methods:** Comprehensive literature review of PubMed database on perioperative use of antithrombotic medication.

**Results/Conclusions:** Perioperative antithrombotic management is largely guided by retrospective studies, consensus recommendations, and trials in other surgical fields due to the limited number of studies in oculoplastic surgery. This review summarizes evidence-based recommendations from related medical specialties and provides context for surgeons to tailor antithrombotic medication management based on patient's individual risk. The decision to continue or cease antithrombotic medications prior to surgery requires a careful understanding of risk: risk of intraoperative or postoperative bleeding versus risk of a perioperative thromboembolic event. Cessation and resumption of antithrombotic medications after surgery should always be individualized based on the patient's thrombotic risk, surgical and postoperative risk of bleeding, and the particular drugs involved, in conjunction with the prescribing doctors. In general, we recommend that high thromboembolic risk patients undergoing high bleeding risk procedures (orbital or lacrimal surgery) may stop antiplatelet agents, direct oral anticoagulants, and warfarin including bridging warfarin with low-molecular weight heparin. Low-risk patients, regardless of

type of procedure performed, may stop all agents. Decision on perioperative management of antithrombotic medications should be made in conjunction with patient's internist, cardiologist, hematologist, or other involved physicians which may limit the role of guidelines depending on patient risk and should be used on a case-by-case basis. Further studies are needed to provide oculofacial-specific evidence-based guidelines.

(*Ophthalmic Plast Reconstr Surg* 2022;38:226–233)

Given the aging of the United States population and the high prevalence of cardiovascular disease, it is not surprising that an increasing proportion of patients presenting to oculofacial surgeons are using antithrombotic medications. One study at a large oculofacial plastic surgery practice found that 40% of patients used at least 1 antithrombotic agent.<sup>1</sup> Antithrombotic medications consist of antiplatelet or anticoagulants; anticoagulants are generally divided into warfarin and heparin or a newer class of direct oral anticoagulants (DOACs). Any of these medications can result in increased bleeding during surgery, leading to increased operative time, intraoperative and postoperative complications, postoperative bruising, and poor postoperative cosmesis. Rarely, orbital compartment syndrome and vision loss may occur. This review aims to provide the evidence of when and which antithrombotic medications should be held before surgery and when they can be safely resumed, highlighting areas of consensus and controversy. Decision-making must be done in conjunction with the patient's primary care doctor, cardiologist, or other involved physicians depending on the patient's risk profile and surgical procedure to be performed.

## METHODS

PubMed searches were conducted using the following search criteria: “blood thinners AND oculoplastic,” “blood thinners AND eyelid,” “blood thinners AND lacrimal,” “blood thinners AND orbit,” “antiplatelet AND oculoplastic,” “direct oral anticoagulant AND oculoplastic,” and “anticoagulant AND oculoplastic”. Targeted searches for relevant articles in related fields such as dermatology, ENT, facial plastic surgery, and plastic surgery literature were carried out. Abstracts were reviewed for relevance. Updated consensus statements from cardiology, anesthesiology, and hematology regarding perioperative risks with antithrombotic agents were also reviewed.

**Classes of Antithrombotic Agents.** There are 3 main classes of antithrombotic agents currently approved by the Food and Drug Ad-

Accepted for publication August 10, 2021.

Supported by unrestricted Grant to the Department of Ophthalmology/Roski Eye Institute at Keck USC School of Medicine from Research to Prevent Blindness, New York, NY and P30EY029220 from the NIH.

The authors have no financial or conflicts of interest to disclose.

This article is adapted from a book chapter, with permission: Pfeiffer ML, Chang JR. Unique Considerations in Upper Facial Surgery. In: Burnstine MA, Dresner SC, Samimi DB, Merritt HA, ed. *Ophthalmic Plastic Surgery of the Upper Face: Eyelid Ptosis, Dermatochalasis, and Eyebrow Ptosis*. New York: Thieme Medical and Scientific Publishers Private Ltd., 2020.

Address correspondence and reprint requests to Michael Burnstine, MD, FACS, USC Roski Eye Institute/Eyestetica, 500 Molino, Suite 107, Los Angeles, CA 90013. E-mail: burnstin@usc.edu

Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Society of Ophthalmic Plastic and Reconstructive Surgery, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

DOI: 10.1097/IOP.0000000000002058

ministration for use in the United States: (1) antiplatelet agents, (2) anticoagulants, and (3) DOACs. Antiplatelet agents permanently or temporarily inhibit platelet aggregation, while anticoagulants impede the formation of fibrin by inhibiting clotting factors through various mechanisms; both result in impaired hemostasis. Many over-the-counter medications and supplements may also impact bleeding, such as nonsteroidal anti-inflammatory drugs (NSAIDs), fish oil, and vitamin E.

**Antiplatelet Agents.** *Antiplatelet agents inhibit platelet aggregation and thrombus formation.* Antiplatelet agents include aspirin, clopidogrel, ticagrelor, cilostazol, dipyridamole, and prasugrel. The 2 most commonly used antiplatelet agents are aspirin and clopidogrel (Plavix). For decades, aspirin has been indicated for both primary and secondary prevention of cardiovascular disease, and many patients also use it for analgesia unrelated to cardiovascular disease. Many patients forget to include aspirin when reporting a medication list, particularly if it is a low dose (e.g., 81 mg or “baby” aspirin).<sup>1</sup> Recently, data have questioned whether aspirin should be used for primary prevention; however, many patients are still taking it for this reason.<sup>2</sup>

Clopidogrel is used as secondary prevention in patients with prior thromboembolic event, prior myocardial infarction, or an implanted device such as a cardiac stent. Aspirin and clopidogrel may be used synergistically (termed dual antiplatelet therapy) in patients at high risk for thromboembolic event. Patients on dual antiplatelet therapy tend to bleed more than patients on a single agent.<sup>3</sup> Dual antiplatelet therapy has been compared with aspirin monotherapy in reducing recurrent stroke in patients with history of stroke and transient ischemic attack.<sup>4,5</sup> A recent systematic review and meta-analysis comparing the efficacy and safety of clopidogrel versus aspirin monotherapy for secondary prevention in patients with prior stroke showed ischemic or hemorrhagic stroke were all significantly lower for clopidogrel monotherapy compared with aspirin.<sup>6</sup>

Nonsteroidal anti-inflammatory drugs (NSAIDs) also inhibit platelet activity, though the effect is usually of shorter duration. NSAIDs act by inhibiting cyclooxygenase (COX), an enzyme with 2 isoforms: COX-1 and COX-2. Both isoforms produce prostaglandins that promote inflammation, fever, and pain. However, only COX-1 is responsible for production of thromboxane A<sub>2</sub>, which is needed for platelet aggregation. NSAIDs may be selective in inhibiting only COX-2 (e.g., celecoxib), or nonselective, inhibiting both COX-1 and COX-2 (e.g., ibuprofen, indomethacin, or naproxen). Thus, nonselective NSAIDs interfere with platelet aggregation, while selective NSAIDs have negligible effects on platelet function.<sup>7</sup>

**Anticoagulants.** *Anticoagulants directly inhibit clotting factors in the coagulation cascade and are indicated in patients with prior pulmonary or venous thromboembolism or prophylactically in the setting of atrial fibrillation, prosthetic heart valves, and rheumatic heart disease.*<sup>8</sup> Warfarin (Coumadin) is the most commonly used oral anticoagulant. Warfarin is a vitamin K antagonist that impairs gamma-carboxylation of factors 2, 7, 9, and 10 resulting in reduced thrombin generation.<sup>9</sup> Warfarin has many food and drug interactions, a narrow therapeutic index, and requires frequent monitoring for dose titration. In the event of emergency surgery or uncontrolled hemorrhage, the anticoagulation effect of warfarin is reversible with vitamin K and fresh frozen plasma.

Unfractionated heparin is an anticoagulant that is delivered intravenously, but its derivative, fractionated or low-molecular weight heparin (LMWH), is available by subcutaneous injection. Enoxaparin is an example of LMWH.

**Direct Oral Anticoagulants.** *The DOACs are alternatives to warfarin in patients with a history of atrial fibrillation or pulmonary or venous thromboembolism.* Examples include apixaban, betrixaban, dabigatran, edoxaban, and rivaroxaban (Table 1). Compared with warfarin, DOACs have a more predictable pharmacologic profile, fewer food and drug interactions, and require no regular monitoring. Compared

**TABLE 1.** Characteristics of anticoagulants

Generic name	Trade name	Metabolism site	Monitor effects	Antidote
Enoxaparin	Lovenox	Liver	PTT	Protamine sulfate
Warfarin	Coumadin	Liver	PT/INR	Vitamin K FFP PCC aPCC <sup>10</sup>
Dabigatran	Pradaxa	Renal	N/A	Dialysis <sup>10</sup> Idarucizumab <sup>10</sup> aPCC (FEIBA) <sup>10</sup> PER977 <sup>10</sup>
Rivaroxaban	Xarelto	Liver, Renal	N/A	PCC <sup>10</sup> aPCC <sup>10</sup> Andexanet alfa <sup>10</sup> PER977 <sup>10</sup>
Apixaban	Eliquis	Liver	N/A	rFVIIa <sup>10</sup> aPCC <sup>10</sup> Andexanet alfa <sup>10</sup> PER977 <sup>10</sup>
Betrixaban	Bevyxxa	Liver, Renal	N/A	Andexanet alfa <sup>10</sup>
Edoxaban	Savaysa	Liver, Renal	N/A	PER977 <sup>10</sup>

aPCC, activated prothrombin complex concentrate; FEIBA, factor VIII inhibitor bypass activity; FFP, fresh frozen plasma; rFVIIa, recombinant activated factor VIIa; INR, international normalized ratio.

with warfarin, they have a more rapid onset of action (average 2–3 hours vs. 3–4 days) and a shorter half-life (average 12 hours vs. 20–60 hours).<sup>11</sup>

## AVAILABLE DATA ON SPECIFIC ANTITHROMBOTICS AND OCULOPLASTIC SURGERY

### Aspirin

There is 1 randomized controlled trial on perioperative management of aspirin in patients undergoing upper blepharoplasty or ptosis repair.<sup>12</sup> This is the only randomized trial on antithrombotic medications in oculoplastic surgery; antithrombotic agents have not been studied prospectively in lacrimal or orbital surgery. Patients were randomized to take aspirin 81 mg or placebo for 7 days preoperatively. Results of 48 patients showed no significant difference in bruising or mild postoperative bleeding.<sup>12</sup> Although there were no instances of postoperative retrobulbar hemorrhage, the study was not powered sufficiently to detect statistical significance in this and other bleeding complications.

### NSAIDs

The effect of nonselective NSAIDs on intra- or postoperative bleeding complications is unclear; some studies suggest increased risk while others suggest there is no increased risk of bleeding complications.<sup>13,14</sup> There is evidence that the selective COX-2 inhibitor celecoxib does not significantly affect platelet function or intraoperative bleeding.<sup>15</sup> Other NSAIDs that affect COX-2 more than COX-1, such as meloxicam and etodolac, have also been shown to have little impact on bleeding risk (Table 2).<sup>16,17</sup>

For post-surgical pain, the intravenous NSAID ketorolac is often offered by the anesthesiologists as an alternative to narcotics, but there have been conflicting studies over whether this may cause increased risk of postoperative bleeding.<sup>18,19</sup> A recent retrospective study and randomized control trial in patients who received intravenous ketorolac in levator advancement surgery found better analgesia and showed

**TABLE 2.** Characteristics of nonsteroidal anti-inflammatory drugs

Generic name	Trade name	Cyclooxygenase (COX) enzyme affected	Half life (hours)	Affects platelet function
Aspirin	Aspirin	COX-1, COX-2	0.25	Yes
Celcoxib	Celebrix	COX-2	11	No
Diclofenac	Catafalm Voltaren Arthrotec (combined with misoprostol)	COX-1, COX-2	1.1	No
Diflunisal	Dolobid	COX-1, COX-2	13	Yes
Etodolac	Lodine, Lodine XL	COX-2	6.5	No
Fenoprofen	Nalfon	COX-2	2.5	No
Flurbiprofen	Ansaid	COX-1	3.5	Yes
Ibuprofen	Advil Motrin Tab-Profen	COX-1, COX-2	2	Yes
Indomethacin	Indocin Indocin SR	COX-1, COX-2	4-5	Yes
Ketoprofen	Orudis KT Oruvail	COX-1, COX-2	1.5	Yes
Ketorolac	Toradol	COX-1, COX-2	5-6	Yes
Meloxicam	Mobic	COX-2	20	No
Nabumetone	Relafen	COX-2	26	No
Naproxen	Aleve, Naprosyn, Anaprox	COX-1, COX-2	14	Yes
Oxaprozin	Daypro	COX-1, COX-2	58	Yes
Piroxicam	Feldene	COX-1, COX-2	57	Yes
Sulindac	Clinoril	COX-1, COX-2	8	No
Tolmetin	Tolectin	COX-1, COX-2	1	Yes

no statistically significant difference in ecchymosis grade and postoperative bleeding when compared with patients who did not receive intravenous ketorolac.<sup>20,21</sup> Another recent prospective study in patients who received intravenous ketorolac during orbital surgery showed a statistically significant reduction in pain without increased risk of bleeding-related complications compared with controls.<sup>22</sup>

### Understanding Risk Profiles

As there is only 1 randomized controlled trial (insufficiently powered to detect rare but serious events like orbital hemorrhage) in oculoplastic surgery, perioperative antithrombotic medication management is guided largely by retrospective studies and consensus recommendations as well as trials in other surgical fields. The decision to cease or continue antithrombotic medication prior to surgery requires an understanding of risk: risk of surgical or postoperative bleeding versus risk of the patient having a thromboembolic event. Although cardiologists and primary care providers are crucial in the decision-making process, oculofacial surgeons must also understand these risks to counsel patients appropriately.

### Understanding Patient Risk of Thromboembolism

Patients are on different antithrombotic medications for different reasons, and some patients are at higher risk than others for thromboembolic events. In patients who stop warfarin for any reason, including perioperatively, there is an approximately 1% risk of a thromboembolic event within 30 days.<sup>23</sup> This risk increases 4-fold in patients with mechanical heart valves.<sup>24</sup> One meta-analysis estimated the additional risk of any vascular event from withholding aspirin for 7 days perioperatively at roughly 0.14%.<sup>25</sup> A recent retrospective study estimated the risk of thromboembolism and major bleeding from withholding DOACs perioperatively to be 1.05% and 0.53%, respectively.<sup>26</sup> Another prospective study in patients withholding DOACs perioperatively estimated rate of arterial thromboembolism to be 0.16% in the apixaban cohort, 0.60% in the dabigatran cohort, and 0.37% in the rivaroxaban cohort.<sup>27</sup>

### Assessment of Surgical Bleeding Risk

Currently, there is no standardized risk assessment that determines the bleeding risk of common oculofacial procedures. Intraoperative bleeding risk is based on the location (proximity to nerves, main blood vessels, or important organs) and extent of tissue damage. Postoperative bleeding risk is based on wound condition after surgery, tissue damage, and tissue perfusion.<sup>28</sup>

### Understanding Surgical Bleeding Risk

The reported risk of vision-threatening hemorrhage intraoperatively or postoperatively for all types of oculoplastic procedures is less than 1%.<sup>29</sup> The risk of vision loss from postoperative hemorrhage varies with procedure, ranging from 0.0045% for blepharoplasty (based on survey data<sup>30</sup>) to 0.24%<sup>31</sup> for orbital surgery.

A prospective study by Custer et al. of 1500 oculoplastics procedures reported an overall rate of severe hemorrhage of 0.4% and “troublesome” intraoperative bleeding of 9%.<sup>29</sup> Patients who continued antiplatelets and anticoagulants had no increased risk of intraoperative bleeding, postoperative bruising, or severe bleeding complications.<sup>29</sup>

Recent studies in lung, orthopedic and abdominal surgery suggest low or negligible bleeding risk with perioperative continuation of aspirin.<sup>32–39</sup> Recommendations in the facial plastics and dermatologic literature also suggest that continuation of antithrombotic medications is associated with low rates of severe hemorrhagic complications.<sup>8,30,40–42</sup> However, it is important to note that results from other specialties may not be transferable due to the unique risk of vision loss with oculoplastic surgeries. The surgeon must assess both the risk and impact of hemorrhage in different oculoplastic procedures based on the nature of incision, depth of dissection, duration of case, ability to easily cauterize or tamponade (e.g., easy with enucleation, difficult with decompression), and the ramifications of bleeding.

Eyelid procedures anterior to the orbital septum such as chalazion excision, eyelid lesion removal, and skin-only blepharoplasty are associated with low risk of vision-threatening hemorrhagic complications, whereas eyelid procedures posterior to

the septum (external ptosis repair and blepharoplasty with fat manipulation) and orbital surgery have higher risk of vision-threatening retrobulbar hemorrhage.<sup>43</sup>

Although orbital surgery in general is higher bleeding risk, orbital surgery in a blind eye or for eye removal is unique in that the risk of vision loss is nonexistent. Therefore, surgeons often choose to continue antithrombotic medications in these cases, cauterize aggressively, and tamponade with a pressure patch postoperatively.<sup>44</sup>

**Balancing Thromboembolic and Bleeding Risks**

Although there are no specific guidelines for oculoplastic surgery, we can extrapolate evidence-based recommendations from other specialties. The American College of Chest Physicians has released guidelines for patients on antithrombotic medication undergoing elective procedures. The oculoplastic surgeon must consult with the patient’s internist, cardiologist, hematologist, or other involved physicians to stratify the patient’s risk (Table 3). If a patient is high-risk, there is a high chance that the patient cannot discontinue antithrombotic medications for any reason, including any oculoplastic surgery. In this case, surgery should be deferred unless (1) bleeding risk for that particular surgery is low, or (2) avoiding surgery creates a high morbidity or mortality risk to the patient. If the patient is low risk, the consulting physician will likely approve perioperative discontinuation of antithrombotic medications.

Once the patient risk is determined, Table 4 helps identify how best to proceed with antithrombotic medications based on the type of surgery to be performed. These guidelines are primarily driven by patient risk: in

high-risk patients undergoing high-risk procedures, guidelines recommend stopping DOACs and warfarin and bridging warfarin with LMWH. Low-risk patients should also stop these medications and do not require bridging. High-risk patients should continue antiplatelet agents when possible, and low-risk patients may stop antiplatelet agents.<sup>48</sup> Patients with history of cardiac stent being treated with dual antiplatelet therapy should continue aspirin perioperatively if possible, whereas clopidogrel and similar agents (P2Y<sub>12</sub> inhibitors) are to be discontinued if warranted by the type of noncardiac elective surgery.<sup>49</sup>

The use of heparin or LMWH as a perioperative substitute for patients on continuous warfarin therapy is a common practice, but high-quality data regarding the safety of heparin bridging therapy is limited, and this practice remains controversial. Some studies have shown an increased risk of bleeding and thromboembolic events in patients undergoing bridging therapy.<sup>50–55</sup> This decision must be discussed with the physician prescribing the warfarin.

**When to Stop Antithrombotic Medications Preoperatively**

Generally, the half-life of the medication is the basis for deciding when to stop that medication prior to surgery (Table 5). Patient kidney and liver function as well as the half-life and COX-2 selectivity<sup>15,17</sup> of their specific NSAID medication should be considered in determining when and whether to hold the medication prior to surgery. Additionally, it is common practice to request that patients stop over the counter NSAIDs, vitamins, and supplements preoperatively. There is little evidence to guide when patients should stop supplements especially as doses and formulations are not FDA-regulated.

**TABLE 3.** Simplified risk stratification of patients for thromboembolism

<b>Highest risk</b>	
Mitral valve prosthesis	
Any caged-ball or tilting disc aortic valve prosthesis	
Recent stroke or TIA (within 6 months)	
Atrial fibrillation with high CHADS <sub>2</sub> score (5 or 6)	
Rheumatic valvular heart disease	
VTE within 3 months	
Severe thrombophilia (e.g., deficiency in protein C, protein S, or antithrombin; antiphospholipid antibodies)	
Recent drug-eluting stent (within 12 months) <sup>45</sup>	
Bare metal stent within 30 days <sup>45</sup>	
LVAD <sup>38</sup>	
<b>Lowest risk</b>	
Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke	
Atrial fibrillation with low CHADS <sub>2</sub> score (0–2)	
Coronary artery disease without stent	
VTE > 12 months previous and no other risk factors	

\*LVAD, these patients should be managed with a heart failure team; some require anticoagulants and heparin bridging while others use antiplatelet agents alone.<sup>46</sup>  
 CHADS<sub>2</sub>, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and stroke; LVAD, left ventricular assist device; TIA, transient ischemic attack; VTE, venous thromboembolism.

**TABLE 4.** How to manage blood thinners perioperatively

Patient risk of thromboembolism	Surgery bleeding risk		
	Minimal (chalazion, eyelid lesion)	Mild (eyelid and brow surgery)	High (lacrimal, orbital, facelift surgery)
Low	Continue all medications	Stop all medications	Stop all medications
High	Continue all medications	Stop DOAC Stop warfarin and bridge with LMWH Continue Aspirin if possible	Stop DOAC Stop warfarin and bridge with LMWH Stop Aspirin

Extrapolated and adapted to oculofacial surgery, based on Spyropoulos et al. (2016).<sup>47</sup>  
 DOAC, direct oral anticoagulant; LMWH, low-molecular weight heparin.



**TABLE 5.** When to stop blood thinners before surgery

Class	Agent	Time to peak effect	When to stop before surgery	Elimination half life
Antiplatelet	Aspirin	5–30 min	7–10 days <sup>56,57</sup>	0.25 hours
	Clopidogrel	0.75 hours	5 days <sup>56,57</sup>	6 hours
Anticoagulant	Warfarin	72–96 hours	3–5 days	20–60 hours
	LMWH	3–5 hours (enoxaparin)	24 hours <sup>58</sup>	4.5–7 hours
DOAC	Dabigatran	1–3 hours	1–5 days* <sup>58</sup>	8–15 hours
	Apixaban	2–4 hours	24–48 hours <sup>58</sup>	7–11 hours
	Rivaroxaban	1–2 hours	24–48 hours <sup>58</sup>	12 hours
	Edoxaban	1–2 hours	24–48 hours <sup>58</sup>	10–14 hours
	Betrixaban	3–4 hours	96 hours	19–27 hours

\*Depending on renal function.

DOAC, direct oral anticoagulant; LMWH, low-molecular weight heparin.

**TABLE 6.** Dietary supplements that potentially influence risk of hemorrhage

Supplements that may increase bleeding risk		Supplements intended to decrease bleeding/bruising risk	
Some evidence	Not well studied	Little evidence of efficacy	
Vitamin E	Dong quai	Arnica montana	
Fish oil/Omega 3	Lycopene	Rhododendron tomentosum	
Ginger	L-Arginine	—	
Ginseng	Taurine	—	
Ginkgo biloba	Passion Flower	—	
Garlic	Chamomile	—	
Selenium	Cinnamon	—	
—	Cayenne Pepper	—	
—	Curcumin	—	
—	Feverfew	—	
—	Tree-ear mushrooms	—	
—	Grape seed extract	—	
—	Echinacea	—	
—	Green tea extract	—	
—	Glucosamine	—	
—	Chondroitin sulfate	—	
—	Coenzyme Q10	—	
—	Policosanol	—	
—	Turmeric	—	
—	Magnesium	—	
—	Biotin	—	

### Supplements and Vitamins

Many supplements have been shown to have anti-thrombotic effect, including but not limited to garlic, Ginkgo biloba, ginger, ginseng, fish oil, vitamin E, and selenium (Table 6). These all affect the coagulation cascade at different points and are reviewed in a recent article.<sup>59</sup> There are anecdotal reports of bleeding episodes on many of these agents, yet more detailed studies have shown equivocal bleeding risk at normal doses but potentially increased risk when used in combination with antithrombotic medications. Perhaps the most well-studied is vitamin E, which inhibits platelet aggregation in a dose-dependent manner at doses higher than 400 IU/day and was found clinically to be linked to hemorrhagic events in atrial fibrillation patients on warfarin.<sup>46</sup>

Conversely, some supplements and medications are taken perioperatively to reduce bleeding and bruising. *Arnica montana* is an herb available in topical and oral formulations marketed for its ability to reduce postoperative ecchymosis. Although there is little evidence for its efficacy in reducing ecchymosis, it is often recommended by surgeons. It has also been studied for its effect on postoperative pain and edema.

One prospective, placebo-controlled study in men undergoing sequential upper blepharoplasty found no difference in ecchymosis or patient comfort in patients on oral *Arnica*.<sup>60</sup> Another study found that *Arnica* reduced edema but not ecchymosis after rhinoplasty and reduced ecchymosis compared with placebo after facelifting.<sup>61</sup> The most recent literature review by American Academy of Ophthalmology does not support the use of *Arnica* for reducing ecchymosis after oculoplastic surgery.<sup>62</sup> Tranexamic acid is an antifibrinolytic agent beginning to be studied in oculoplastic surgery<sup>63</sup> but has been used in trauma, orthopedic, cardiac, and recently (off-label) in plastic surgery to reduce blood loss and possibly to improve postoperative edema.<sup>64</sup>

### Timing to Resume Antithrombotic Medications Postoperatively

There is a dearth of studies on when to resume postoperative antithrombotic therapy. We suggest that, if the surgery was not complicated by bleeding, one can resume warfarin on the evening of surgery.<sup>65</sup> Given warfarin's delayed onset of action of 2 to 5 days, it can take up to 7 to 14 days to attain a patients' therapeutic international normalized ratio (INR) with their usual maintenance dosing.<sup>66</sup>

Based on a recent prospective study, we recommend resuming DOACs (dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban) on postoperative day 1 after low bleeding risk procedures (eyelid procedures) and postoperative days 2 to 4 (depending on agent and renal function) after high bleeding risk procedures (lacrimal, orbit, and facelift procedures).<sup>27,67</sup> In this study, hypertension was the only modifiable risk factor in predicting bleeding events.<sup>67</sup>

Antiplatelet therapy should be resumed on the evening of surgery if the surgery did not have any bleeding complications.<sup>49,68,69</sup>

Fibrinolysis and fibrin formation is a tightly regulated physiological process. Disturbance in the balance between fibrin formation and fibrinolysis by antithrombotic medications can lead to enhancement of clot lysis. Studies suggest that dabigatran, rivaroxaban, and apixaban increase clot lysis permeability and decrease time clot lysis time when compared with control clots in absence of anticoagulants.<sup>70–73</sup> Studies also suggest warfarin increases plasma clot porosity as early as 3 days after initiating treatment, reaching the plateau value after 7 days.<sup>74</sup> A study analyzing clots *in vitro* demonstrated aspirin to loosen fibrin networks, enhance clot lysis and lower clot rigidity.<sup>75</sup> There is currently no data that demonstrates clopidogrel to have an effect on plasma clot properties.

## CONCLUSION

Currently, no guidelines exist regarding perioperative antithrombotic use in oculofacial plastic surgery. As a result, a wide spectrum of practice patterns exist. Guidelines from related medical specialties provide evidence-based or expert consensus recommendations that may guide surgeons. The oculofacial surgeon, in close conjunction with the patient's other physicians, should consider the surgical risks of bleeding complications and patient-specific risk factors when managing anti-thrombotics. Oculofacial surgery is unique in the risk of vision loss from orbital hemorrhage, and this must be considered. One should refer to the most updated consensus guidelines for anti-thrombotic medications management in surgery and also seek input from the patient's internist, cardiologist, and hematologist to tailor antithrombotic management to each patient's individual risk.

## REFERENCES

- Kent TL, Custer PL. Bleeding complications in both anticoagulated and nonanticoagulated surgical patients. *Ophthalmic Plast Reconstr Surg* 2013;29:113–117.
- Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. *Am Hear Assoc* 2019;140:e596–e646.
- Huang Y, Li M, Li JY, et al. The efficacy and adverse reaction of bleeding of clopidogrel plus aspirin as compared to aspirin alone after stroke or TIA: a systematic review. *PLoS One* 2013;8:e65754.
- Wang Y, Pan Y, Zhao X, et al; CHANCE Investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack (CHANCE) trial: one-year outcomes. *Circulation* 2015;132:40–46.
- Wang Y, Wang Y, Zhao X, et al; CHANCE Investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med* 2013;369:11–19.
- Paciaroni M, Ince B, Hu B, et al. Benefits and risks of clopidogrel vs. aspirin monotherapy after recent ischemic stroke: a systematic review and meta-analysis. *Cardiovasc Ther* 2019;2019:1607181.
- Knijff-Dutmer EA, Kalsbeek-Batenburg EM, Koerts J, et al. Platelet function is inhibited by non-selective non-steroidal anti-inflammatory drugs but not by cyclo-oxygenase-2-selective inhibitors in patients with rheumatoid arthritis. *Rheumatology (Oxford)* 2002;41:458–461.
- Callahan S, Goldsberry A, Kim G, et al. The management of antithrombotic medication in skin surgery. *Dermatol Surg* 2012;38:1417–1426.
- Wypasek E, Mazur P, Bochenek M, et al. Factors influencing quality of anticoagulation control and warfarin dosage in patients after aortic valve replacement within the 3 months of follow up. *J Physiol Pharmacol* 2016;67:385–393.
- Yates SW. Interrupting anticoagulation in patients with nonvalvular atrial fibrillation. *P T* 2014;39:858–880.
- Esparaz ES, Sobel RK. Perioperative management of anticoagulants and antiplatelet agents in oculoplastic surgery. *Curr Opin Ophthalmol* 2015;26:422–428.
- Winkler KP, Beaulieu R, Beville L, et al. Effects of aspirin on postoperative bruising and bleeding complications in upper eyelid surgery. *Ophthalmic Plast Reconstr Surg* 2020;36:575–578.
- Gobble RM, Hoang HLT, Kachniarz B, et al. Ketorolac does not increase perioperative bleeding: a meta-analysis of randomized controlled trials. *Plast Reconstr Surg* 2014;133:741–755.
- Kelley BP, Bennett KG, Chung KC, et al. Ibuprofen may not increase bleeding risk in plastic surgery: a systematic review and meta-analysis. *Plast Reconstr Surg* 2016;137:1309–1316.
- Teerawattananon C, Tantayakom P, Suwanawiboon B, et al. Risk of perioperative bleeding related to highly selective cyclooxygenase-2 inhibitors: a systematic review and meta-analysis. *Semin Arthritis Rheum* 2017;46:520–528.
- Warner TD, Giuliano F, Vojnovic I, et al. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full *in vitro* analysis. *Proc Natl Acad Sci USA* 1999;96:7563–7568.
- Van Ryn J, Kink-Eiband M, Kuritsch I, et al. Meloxicam does not affect the antiplatelet effect of aspirin in healthy male and female volunteers. *J Clin Pharmacol* 2004;44:777–784.
- Chan DK, Parikh SR. Perioperative ketorolac increases post-tonsillectomy hemorrhage in adults but not children. *Laryngoscope* 2014;124:1789–1793.
- Moeller C, Pawlowski J, Pappas AL, et al. The safety and efficacy of intravenous ketorolac in patients undergoing primary endoscopic sinus surgery: a randomized, double-blinded clinical trial. *Int Forum Allergy Rhinol* 2012;2:342–347.
- Chang M, Gould A, Gur Z, et al. Does intraoperative ketorolac increase bleeding in oculoplastic surgery? *Ophthalmic Plast Reconstr Surg* 2020;36:355–358.
- Wladis EJ, Dennett KV, Chen VH, et al. Preoperative intravenous ketorolac safely reduces postoperative pain in levator advancement surgery. *Ophthalmic Plast Reconstr Surg* 2018;35:357–359.
- Wladis EJ, Lee KW, De A. Intravenous ketorolac reduces pain score and opioid requirement in orbital surgery. *Ophthalmic Plast Reconstr Surg* 2020;36:132–134.
- Garcia DA, Regan S, Henault LE, et al. Risk of thromboembolism with short-term interruption of warfarin therapy. *Arch Intern Med* 2008;168:63–69.
- Cannegieter SC, Rosendaal FR, Briët E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. *Circulation* 1994;89:635–641.
- Burger W, Chemnitz JM, Kneissl GD, et al. Low-dose aspirin for secondary cardiovascular prevention – cardiovascular risks after its perioperative withdrawal versus bleeding risks with its continuation – review and meta-analysis. *J Intern Med* 2005;257:399–414.
- Shaw J, de Wit C, Le Gal G, et al. Thrombotic and bleeding outcomes following perioperative interruption of direct oral anticoagulants in patients with venous thromboembolic disease. *J Thromb Haemost* 2017;15:925–930.
- Douketis JD, Spyropoulos AC, Anderson JM, et al. The perioperative anticoagulant use for surgery evaluation (PAUSE) study for patients on a direct oral anticoagulant who need an elective surgery or procedure: design and rationale. *Thromb Haemost* 2017;117:2415–2424.
- Thiele T, Kaftan H, Hosemann W, et al. Hemostatic management of patients undergoing ear-nose-throat surgery. *GMS Curr Top Otorhinolaryngol Head Neck Surg* 2015;14:Doc07.
- Custer PL, Trinkaus KM. Hemorrhagic complications of oculoplastic surgery. *Ophthalmic Plast Reconstr Surg* 2002;18:409–415.
- Hass AN, Penne RB, Stefanyshyn MA, et al. Incidence of post-blepharoplasty orbital hemorrhage and associated visual loss. *Ophthalmic Plast Reconstr Surg* 2004;20:426–432.

31. Jacobs SM, McInnis CP, Kapeles M, et al. Incidence, risk factors, and management of blindness after orbital surgery. *Ophthalmology* 2018;125:1100–1108.
32. Yoshimoto Y, Fujikawa T, Tanaka A, et al. Optimal use of antiplatelet agents, especially aspirin, in the perioperative management of colorectal cancer patients undergoing laparoscopic colorectal resection. *World J Surg Oncol* 2019;17:92.
33. Sakamoto Y, Fujikawa T, Kawamura Y. Safety of elective laparoscopic cholecystectomy in patients with antiplatelet therapy: lessons from more than 800 operations in a single tertiary referral institution. *Asian J Endosc Surg* 2020;13:33–38.
34. Ono K, Hidaka H, Sato M, et al. Preoperative continuation of aspirin administration in patients undergoing major abdominal malignancy surgery. *J Anesth* 2019;33:90–95.
35. Stamenovic D, Schneider T, Messerschmidt A. Aspirin for patients undergoing major lung resections: hazardous or harmless? *Interact Cardiovasc Thorac Surg* 2019;28:535–541.
36. Chen CF, Tsai SW, Wu PK, et al. Does continued aspirin monotherapy lead to a higher bleeding risk after total knee arthroplasty? *J Chin Med Assoc* 2019;82:60–65.
37. Cheng A, Poon MTC, Demetriades AK. Aspirin therapy discontinuation and intraoperative blood loss in spinal surgery: a systematic review. *Neurosurg Rev* 2018;41:1029–1036.
38. Zhang C, Wang G, Liu X, et al. Safety of continuing aspirin therapy during spinal surgery: a systematic review and meta-analysis. *Medicine (Baltimore)* 2017;96:e8603.
39. Carneiro A, Cha JD, Baccaglini W, et al. Should aspirin be suspended prior to robot-assisted radical prostatectomy? A systematic review and meta-analysis. *Ther Adv Urol* 2019;11:1756287218816595.
40. Bordeaux JS, Martires KJ, Goldberg D, et al. Prospective evaluation of dermatologic surgery complications including patients on multiple antiplatelet and anticoagulant medications. *J Am Acad Dermatol* 2011;65:576–583.
41. Alcalay J, Alcalay R. Controversies in perioperative management of blood thinners in dermatologic surgery: continue or discontinue? *Dermatol Surg* 2004;30:1091–1094; discussion 1094.
42. Antia C, Hone N, Gloster H. Perioperative complications with new oral anticoagulants dabigatran, apixaban, and rivaroxaban in Mohs micrographic surgery: a retrospective study. *J Am Acad Dermatol* 2017;77:967–968.
43. Makuloluwa AK, Tiew S, Briggs M. Peri-operative management of ophthalmic patients on anti-thrombotic agents: a literature review. *Eye (London)* 2019;33:1044–1059.
44. Ing E, Douketis J. New oral anticoagulants and oculoplastic surgery. *Can J Ophthalmol* 2014;49:123–127.
45. Ghadimi K, Thompson A. Update on perioperative care of the cardiac patient for noncardiac surgery. *Curr Opin Anaesthesiol* 2015;28:342–348.
46. Pastori D, Carnevale R, Cangemi R, et al. Vitamin E serum levels and bleeding risk in patients receiving oral anticoagulant therapy: a retrospective cohort study. *J Am Heart Assoc* 2013;2:e000364.
47. Spyropoulos AC, Al-Badri A, Sherwood MW, et al. Perioperative management of patients receiving a vitamin K antagonist or a direct oral anticoagulant requiring an elective procedure or surgery. *J Thromb Haemost* 2016;14:875–885.
48. Darvish-Kazem S, Gandhi M, Marcucci M, et al. Perioperative management of antiplatelet therapy in patients with a coronary stent who need noncardiac surgery: a systematic review of clinical practice guidelines. *Chest* 2013;144:1848–1856.
49. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: a Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: an Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. *Circulation* 2016;134:e123–e155.
50. Ayoub K, Nairooz R, Almomani A, et al. Perioperative heparin bridging in atrial fibrillation patients requiring temporary interruption of anticoagulation: evidence from meta-analysis. *J Stroke Cerebrovasc Dis* 2016;25:2215–2221.
51. Birnie DH, Healey JS, Wells GA, et al; BRUISE CONTROL Investigators. Pacemaker or defibrillator surgery without interruption of anticoagulation. *N Engl J Med* 2013;368:2084–2093.
52. Douketis JD, Spyropoulos AC, Kaatz S, et al; BRIDGE Investigators. Perioperative bridging anticoagulation in patients with atrial fibrillation. *N Engl J Med* 2015;373:823–833.
53. Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(suppl 2):e326S–e350S.
54. Regan DW, Kashiwagi D, Dougan B, et al. Update in perioperative medicine: practice changing evidence published in 2016. *Hosp Pract (1995)* 2017;45:158–164.
55. Siegal D, Yudin J, Kaatz S, et al. Periprocedural heparin bridging in patients receiving vitamin K antagonists: systematic review and meta-analysis of bleeding and thromboembolic rates. *Circulation* 2012;126:1630–1639.
56. Bonhomme F, Hafezi F, Boehlen F, et al. Management of anti-thrombotic therapies in patients scheduled for eye surgery. *Eur J Anaesthesiol* 2013;30:449–454.
57. McClellan AJ, Flynn HW, Jr, Smiddy WE, et al. The use of perioperative antithrombotics in posterior segment ocular surgery. *Am J Ophthalmol* 2014;158:858–859.
58. Barnes GD, Moulard E. Peri-procedural management of oral anticoagulants in the DOAC era. *Prog Cardiovasc Dis* 2018;60:600–606.
59. Stanger MJ, Thompson LA, Young AJ, et al. Anticoagulant activity of select dietary supplements. *Nutr Rev* 2012;70:107–117.
60. Kotlus BS, Heringer DM, Dryden RM. Evaluation of homeopathic *Arnica montana* for ecchymosis after upper blepharoplasty: a placebo-controlled, randomized, double-blind study. *Ophthalmic Plast Reconstr Surg* 2010;26:395–397.
61. Iannitti T, Morales-Medina JC, Bellavite P, et al. Effectiveness and safety of *Arnica montana* in post-surgical setting, pain and inflammation. *Am J Ther* 2016;23:e184–e197.
62. Tao JP, Aakalu VK, Freitag SK, et al. Homeopathic agents or vitamins in reducing ecchymosis after oculofacial surgery: a report by the American Academy of Ophthalmology. *Ophthalmology* 2021;S0161-6420(21)00376-6.
63. Sagiv O, Rosenfeld E, Kalderon E, et al. Subcutaneous tranexamic acid in upper eyelid blepharoplasty: a prospective randomized pilot study. *Can J Ophthalmol* 2018;53:600–604.
64. Ghavimi MA, Taheri Taleh K, Ghoreishizadeh A, et al. Efficacy of tranexamic acid on side effects of rhinoplasty: a randomized double-blind study. *J Craniomaxillofac Surg* 2017;45:897–902.
65. Schulman S, Hwang HG, Eikelboom JW, et al. Loading dose vs. maintenance dose of warfarin for reinitiation after invasive procedures: a randomized trial. *J Thromb Haemost* 2014;12:1254–1259.
66. Kovacs MJ, Kearon C, Rodger M, et al. Single-arm study of bridging therapy with low-molecular-weight heparin for patients at risk of arterial embolism who require temporary interruption of warfarin. *Circulation* 2004;110:1658–1663.
67. Tafur AJ, Clark NP, Spyropoulos AC, et al. Predictors of bleeding in the perioperative anticoagulant use for surgery evaluation study. *J Am Heart Assoc* 2020;9:e017316.
68. Kozek-Langenecker SA, Ahmed AB, Afshari A, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: first update 2016. *Eur J Anaesthesiol* 2017;34:332–395.
69. Godier A, Fontana P, Motte S, et al; members of the French Working Group on perioperative haemostasis (GIHP). Management of antiplatelet therapy in patients undergoing elective invasive procedures. Proposals from the French Working Group on perioperative haemostasis (GIHP) and the French Study Group on thrombosis and haemostasis (GFHT). In collaboration with the French Society for Anaesthesia and Intensive Care Medicine (SFAR). *Anaesth Crit Care Pain Med* 2018;37:379–389.

70. Ammollo CT, Semeraro F, Incampo F, et al. Dabigatran enhances clot susceptibility to fibrinolysis by mechanisms dependent on and independent of thrombin-activatable fibrinolysis inhibitor. *J Thromb Haemost* 2010;8:790–798.
71. Varin R, Mirshahi S, Mirshahi P, et al. Improvement of thrombolysis by rivaroxaban, an anti-Xa inhibitor. Potential therapeutic importance in patients with thrombosis. *Blood* 2008;112:3031.
72. Janion-Sadowska A, Natorska J, Siudut J, et al. Plasma fibrin clot properties in the G20210A prothrombin mutation carriers following venous thromboembolism: the effect of rivaroxaban. *Thromb Haemost* 2017;117:1739–1749.
73. Blombäck M, He S, Bark N, et al. Effects on fibrin network porosity of anticoagulants with different modes of action and reversal by activated coagulation factor concentrate. *Br J Haematol* 2011;152:758–765.
74. Ząbczyk M, Majewski J, Karkowski G, et al. Vitamin K antagonists favourably modulate fibrin clot properties in patients with atrial fibrillation as early as after 3 days of treatment: relation to coagulation factors and thrombin generation. *Thromb Res* 2015;136:832–838.
75. Svensson J, Bergman AC, Adamson U, et al. Acetylation and glycation of fibrinogen *in vitro* occur at specific lysine residues in a concentration dependent manner: a mass spectrometric and isotope labeling study. *Biochem Biophys Res Commun* 2012;421:335–342.