Peri-operative management of ophthalmic patients on anti-thrombotic agents: a literature review

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Abstract

There is variability in the management of ophthalmic patients on anti-thrombotic agents (antiplatelets and anticoagulants) during the peri-operative period. A survey carried out in a UK teaching hospital on a cohort of ophthalmologists showed majority were comfortable with antiplatelet management but there was variability in managing patients on warfarin and direct oral anticoagulants (DOACs); 40% were unaware of existing guidelines. We aim to review the recommendations in the literature with regards to managing anti-thrombotic agents during the peri-operative period of ophthalmic surgery. We reviewed incidences of complications, specifically, the haemorrhagic complications associated. Pubmed search was carried out on relevant keywords from January 2007 to August 2017. All relevant UK guidelines including the Royal College of Ophthalmologists and British Society of Haematology were reviewed. Literature recommendations for routine cataract surgery under topical or sub-Tenon's anaesthesia would be to continue all anti-thrombotic agents. For sharp needle anaesthesia, avoidance of dual antiplatelet therapy was recommended and warfarin could be continued if INR within therapeutic range. Recommendations for surgeries in glaucoma, vitreo-retinal, oculoplastic and lacrimal; and strabismus are presented. No evidence was found for corneal surgery. Haemorrhagic complications are reported in all groups. Limitations of this review include the retrospective nature, lack of randomized control trials and the limited evidence regarding DOACs. It is important for ophthalmologists to be aware of and balance the risk of thromboembolic events and risks of haemorrhagic complications for ophthalmic surgery. A multi-disciplinary approach is recommended for complex cases.

Introduction

Anti-thrombotic agents, used in the prevention and treatment of cardiovascular and ischaemic cerebral diseases, are classified into antiplatelet and anticoagulant agents. With an ageing population, there is an increasing prevalence of ophthalmic patients on anti-thrombotic agents. Oh et al. reported 14.6, 28.5 and 32.3 of patients undergoing vitreoretinal surgery were on antiplatelet agents in 1993, 2004 and 2008, respectively [1]. In this study, warfarin use

(an anticoagulant) was reported in 0.9%, 3.9% and 3.6% of patients in 1993, 2004 and 2008, respectively [1].

Continuing anti-thrombotic agents peri-operatively may increase the risk of potentially sight-threatening haemorrhagic complications, whereas discontinuing these medications may increase the risk of life-threatening thromboembolic events. Therefore, it is important to understand the indications of anti-thrombotic agents and when it may be safe to discontinue them peri-operatively. Similarly, it is essential to stratify ophthalmic surgeries depending on the risk of peri-operative haemorrhagic complications. The British Society of Haematology (BSH) recommends that the surgeon assesses the risk of haemorrhagic complications for individual patients, discuss these risks with the patient and record the peri-operative and discharge plan in patient's notes [2]. It is vital that a multi-disciplinary approach is taken when complex situations arise to ensure that the safest option is chosen for each patient depending on their individual thromboembolic and haemorrhagic risk factors.

The first aim of this review is to discuss the different types of antiplatelet and anticoagulant agents, their

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indications and when patients should be considered for bridging anticoagulation. Our second aim is to discuss the reported incidences of haemorrhagic complications associated with the different types of ophthalmic surgeries and to review the recommendations made in the literature.

Methods

We reviewed the guidelines produced by the BSH, Royal College of Ophthalmologists (RCOphth) and our local Trust on peri-operative management of patients on anti-thrombotic agents. We also undertook a literature review using relevant keywords on articles published in English from January 2007 to August 2017.

Antiplatelet Agents

Various antiplatelet agents are prescribed for various indications, predominantly for the treatment and primary and secondary prevention of cardiovascular and ischaemic cerebral diseases (Fig. 1). Aspirin is a cyclooxygenase-1 (COX1) inhibitor, which in turn inhibits thromboxane A₂ formation and therefore platelet aggregation [3, 4]. Clopidogrel, prasugrel and ticagrelor inhibit P2Y₁₂ receptors (ADP receptors) found in platelets that are involved in platelet aggregation [5]. Clopidogrel and prasugrel irreversibly inhibit this receptor, whereas ticagrelor reversibly inhibits the same receptor on platelets [4, 6]. Dual antiplatelet therapy (DAPT), a combination of aspirin and a P2Y₁₂ receptor inhibitor, is indicated following acute coronary syndromes and coronary artery stenting [2]. Dipyridamole is another antiplatelet agent that inhibits platelet aggregation by inhibiting phosphodiesterase thereby increasing cAMP (cyclic adenosine monophosphate) levels in platelets [7].

The BSH guidelines recommend continuing aspirin indicated for secondary prevention of cardiovascular diseases if patients are undergoing low haemorrhagic risk procedures and discontinuing if undergoing high haemorrhagic risk procedures [2]. A randomized, double-blind, placebo-controlled study has shown that discontinuing aspirin for 7 days pre-operatively and re-starting 3 days post-operatively resulted in a significant increase to Major Adverse Cardiac Events (MACE) (9.0% vs. 1.8%, $p = 0.02$) and no significant difference to the peri-operative blood loss

in patients with stable cardiovascular disease undergoing high-risk elective surgery compared to those that continued aspirin peri-operatively [2]. The increased risk of MACE in patients who discontinued antiplatelet agents has been suggested to be due to a rebound platelet re-activity as well as due to the pro-inflammatory and pro-thrombotic effects of surgery itself [8]. There is limited evidence on clopidogrel and it has been suggested to follow the same guidelines as aspirin in patients on clopidogrel [2].

In contrast to aspirin monotherapy, DAPT has been associated with an increased risk of haemorrhagic complications during surgery (14.7% vs. 4.1%) [2]. Patients undergoing coronary artery bypass graft surgery were found to have similar incidences of haemorrhagic events with aspirin and ticagrelor dual therapy, but increased risk with aspirin and prasugrel dual therapy, when compared to patients on aspirin and clopidogrel dual therapy [2]. DAPT is indicated for patients following acute coronary syndromes and coronary artery stenting for at least 4 weeks following bare metal stent insertion and for 12 months following drug-eluting stent insertion [2]. The risk of MACE is greatest within the first month after stent insertion and gradually reduces over the first one year [2]. Early discontinuation of DAPT following stent insertion has been associated with ischaemic complications: discontinuing clopidogrel within 30 days has been shown to increase the risk of death by ten-folds in the following 11 months compared to those who continued the medication [9]. Therefore, BSH guidelines recommend that DAPT is continued in patients undergoing “very low bleeding risk” procedures, whereas the P2Y₁₂ receptor inhibitor may be discontinued temporarily with continuation of aspirin in patients undergoing “low bleeding risk” procedures who have a low thromboembolic risk [2]. If patients are at risk of high thromboembolic risk, elective surgery should be postponed until the patient is deemed to have a low risk of thromboembolism, that is a minimum of 4 to 6 weeks (preferably 3 months) after bare metal stent insertion and 6 months (preferably 12 months) after drug-eluting stent insertion [2]. After this high-risk period, aspirin should be continued in these patients, whereas the P2Y₁₂ receptor inhibitors may be discontinued temporarily [2]. If patient requires urgent surgery, aspirin is to be continued with temporary discontinuation of the P2Y₁₂ receptor inhibitor (clopidogrel/ticagrelor for 5 days and prasugrel for 7 days pre-operatively) [2]. This is recommended for patients undergoing urgent intracranial, spinal canal and posterior eye chamber surgery who are within the high thromboembolic risk period [2]. In patients with high thromboembolic risks requiring high bleeding risk surgery that is urgent, bridging with a parenteral short-acting glycoprotein IIb/IIIa inhibitor (tirofiban or eptifibatide) should be considered while P2Y₁₂ receptor inhibitors are discontinued [2].

Fig. 1 Mechanisms of action of antiplatelet agents

Anticoagulant Agents

Warfarin

Warfarin inhibits vitamin K-dependent gamma-carboxylation of coagulation factors II, VII, IX and X (Fig. 2) [10]. It also inhibits the formation of proteins C and S of the coagulation pathway [10]. Warfarin has an approximate half-life of thirty-six hours and therefore needs to be discontinued 5 days pre-operatively to ensure normal haemostasis and international normalized ratio (INR) needs to be checked on the day of surgery [2]. Due to slow onset of action, warfarin may be restarted on the evening of surgery or the next day if adequate haemostasis has been achieved [2].

Direct Oral Anticoagulants (DOACs)

DOACs (dabigatran, rivaroxaban, apixaban, edoxaban) are indicated for stroke prevention in non-valvular atrial fibrillation (AF) and treatment and prevention of deep venous thrombosis (DVT) and pulmonary embolism (PE) [2]. They are given as a fixed once or twice daily dose regimens and do not require regular laboratory monitoring [6]. Unlike warfarin, they have fewer food and drug interactions [6]. However, renal function needs to be monitored as most are excreted via the kidneys, especially dabigatran (80% excreted via kidneys) [6, 9]. Major limitations of DOACs are that they lack a reversing agent in the event of a haemorrhagic complication and currently there are no standard tests to measure the anticoagulant effect [6]. Idarucizumab is an approved reversal agent for dabigatran and andexanet, when available, can be used to reverse apixaban, rivaroxaban or edoxaban [2].

The RE-LY study included 4951 patients whose dabigatran was temporarily discontinued for 1 to 5 days prior to various surgical and invasive procedures, depending on the renal function [2, 11]. Of the study population, 9.3% underwent cataract surgery and all patients were monitored for up to 30 days post operatively. The authors reported that there was no statistically significant difference in the incidence of major haemorrhages between the dabigatran group and warfarin group (discontinued 5 days pre-operatively).

Fig. 2 Mechanisms of action of anticoagulant agents

The incidences of stroke and systemic embolism were 0.5% in each group during the first 30 days of discontinuation [2, 11]. Another multicentre prospective study that included 324 standard risk and 217 high haemorrhagic risk procedures reported an incidence rate of 1.8% for major bleeding (0.7–3.0%) and 0.2% (0–0.5%) for thromboembolic events in the first 30 days of discontinuation of dabigatran pre-operatively [2].

The Rocket-AF study reported no significant difference in the incidences of haemorrhagic or thromboembolic events in patients who underwent 2980 procedures (8% ophthalmic procedures) when rivaroxaban was discontinued for three or more days compared to when warfarin was discontinued [2]. The Aristotle study investigated 9260 procedures (8% ophthalmic procedures) of which 60% were undertaken in patients who discontinued apixaban [2]. Most of the procedures were deemed low risk of haemorrhage. There were no significant differences to the incidence of haemorrhagic complications in patients taking apixaban compared to warfarin irrespective of whether or not anticoagulation was discontinued [2].

Sun et al. reported findings of a systematic review and meta-analysis of twelve phase 3 randomised controlled trials (RCTs) published until August 2016 on events of intraocular haemorrhage in patients on DOACs [12]. This study included 102 627 patients on DOACs (4 studies on rivaroxaban, 4 on dabigatran, 2 on apixaban and 2 on edoxaban) compared to warfarin that were indicated for AF or venous thromboembolism (VTE). Their findings showed that there is a 22% relative reduction in intraocular haemorrhagic events in patients on DOACs compared to those on warfarin (risk ratio 0.78, 95% CI 0.61–0.99). This was irrespective of the indication for DOAC and type of DOAC used by the patient [12]. The BSH guidelines for peri-operative management of DOACs are shown in Table 1.

Bridging Anticoagulants

There is evidence that temporary discontinuation of anticoagulant agents lead to a transient hypercoagulable state with a rapid increase in clotting factors, thus increasing the risk of thromboembolic events [13]. Bridging anticoagulation is the introduction of a therapeutic dose short-acting anticoagulant agent during temporary interruption of oral anticoagulants described above [9]. These short-acting anticoagulants are sub-cutaneous low molecular weight heparin (LMWH) and intravenous unfractionated heparin (UFH) [9]. They inhibit thrombin (factor IIa) and Xa, however, LMWH predominantly inhibit factor Xa than IIa [14]. Due to the shorter half-lives of DOACs, it has been suggested that bridging anticoagulation is not required peri-operatively when DOACs are temporarily discontinued [6, 9]. If bridging anticoagulation is given peri-operatively, it is important to

Table 1 BSH guidelines on peri-operative management of direct oral anticoagulant agents

DOAC	Renal function CrCL (mL/min)	Risk of haemorrhage associated with surgery	
		Low	High
Dabigatran	≥80	Stop 24 h pre-operatively	Stop 48 h pre-operatively
	≥50 and <80	24–48 h pre-operatively	48–72 h pre-operatively
	≥30 to <50	48–72 h pre-operatively	72–96 h pre-operatively
Rivaroxaban Apixaban Edoxaban	≥30	24 h pre-operatively	48 h pre-operatively
	<30	48 h pre-operatively	72 h pre-operatively

Re-start DOACs 6–12 h and 48 h after low and high-risk procedures, respectively, if adequate haemostasis is achieved

If patient is at high risk of thromboembolic events, prophylactic anticoagulation may be considered prior to re-starting full therapeutic dose of DOAC

CrCL Creatinine clearance (mL/min)

note that DOACs and bridging anticoagulation must not be given simultaneously [8]. This is in contrast to warfarin, when bridging anticoagulation is given post-operatively until INR is within therapeutic level after re-starting warfarin. Although the evidence from RCTs are limited, there are evidence from systematic reviews and meta-analyses that show that bridging anticoagulation is associated with an increased risk of haemorrhage and with uncertain absolute reduction of thromboembolic events [2, 9].

Guidelines on the use of bridging anticoagulation as recommended by BSH and our local Trust guidelines are shown in Fig. 3. The requirement for bridging anticoagulation in the presence of mechanical heart valves (MHV) depend on the location of the valve, type of valve and co-existence of stroke risk factors [2]. For patients with AF the CHADS₂ score (congestive cardiac failure, hypertension, age ≥ 75, diabetes mellitus and previous stroke or transient ischaemic attack (TIA)) can be used to predict the risk of stroke and select patients who may require bridging anticoagulation [2]. For patients with acute VTE the risk of recurrence without anticoagulation is more than 10% per year in the first 3 months and surgery will increase this risk further [9]. Beyond this high-risk period, the anticoagulation is for secondary prevention when prophylactic dose of LMWH can be given instead of treatment dose until the INR is within therapeutic range [9]. Bridging therapy should also be considered for patients who have had previous VTE while on therapeutic anticoagulation who now have a target INR of 3.5, active metastatic cancers and patients with thrombophilia [2, 9].

The last dose of therapeutic LMWH should be given at least 24 hours pre-operatively and some recommend giving half the therapeutic dose. Post-operatively, bridging anticoagulation should not be started at least after 48 hours of high-risk surgery and only when adequate haemostasis has been achieved [2, 9]. However, prophylactic doses may be given within the first 48 hours if indicated [2]. Bridging anticoagulation is to be continued

until INR is within therapeutic range after re-starting warfarin post-operatively [9].

Haemorrhagic Complications Associated With Ophthalmic Surgeries – Risk Stratification

Ophthalmic Anaesthesia

Cataract surgery is the most (Table 2) commonly performed ophthalmic surgery in the UK [15]. The number of surgeries has quadrupled from approximately 100 000 per year in 1990 to over 400 000 per year in England between 2016 and 2017 [15–17]. Almost 97% of these operations are performed under local anaesthesia [18]. A recent British Ophthalmological Surveillance Unit (BOSU) study showed that the current usage of local anaesthesia are 39% for topical (with or without intracameral), 51% for sub-Tenon's, 9% for peribulbar, and 1% for retro-bulbar anaesthesia [18]. The latest NICE guidelines recommend offering patients sub-Tenon's, or topical (with or without intracameral) anaesthesia for patient undergoing cataract surgery [17]. If these are contraindicated, offer peri-bulbar anaesthesia. However, they do not recommend retro-bulbar anaesthesia for patients undergoing cataract surgery.

The literature to date reports no sight-threatening complications associated with local anaesthetic blocks in patients who are on single antiplatelet agents or on anticoagulant agents. Most complications reported are sub-conjunctival haemorrhages that resolve spontaneously without affecting vision. Benzmira et al. reported an increased risk of self-limiting sub-conjunctival haemorrhages with clopidogrel (4.4%) and warfarin (3.7%) compared to non-anti-thrombotic users (1.7%) who had sub-Tenon's or sharp needle anaesthesia [19]. However, the authors did not clarify if these anti-thrombotic agents were continued or discontinued peri-operatively. Kobayashi et al. reported the incidence sub-conjunctival haemorrhages to be

Fig. 3 Indications for bridging anticoagulation (BSH and local Trust guidelines, Kong 2015)

(1) MECHANICAL HEART VALVES		
*NOTE: if type of valve cannot be verified start bridging anticoagulation		
High risk	<ul style="list-style-type: none"> Recent stroke/TIA (within 6 months) All mitral valves Caged-ball^a or single-leaflet tilting disc^a aortic valve 	Bridging strongly recommended
Moderate risk	Bileaflet tilting disc aortic valve ^c and one or more stroke risk factors ^d	Bridging should be considered
Low risk	Bileaflet tilting disc aortic valve without AF and no other risk factors for stroke ^d	Bridging optional
^a Starr-Edwards ^b Bjork-Shiley, Medtronic-Hall or Omniscarbon valve ^c St Jude or Carbomedics valve ^d Stroke risk factors: AF, previous stroke/TIA, congestive heart failure/reduced left ventricular ejection fraction, age >75 years, hypertension, diabetes mellitus		
(2) ATRIAL FIBRILLATION		
High risk	<ul style="list-style-type: none"> Recent stroke/TIA (within 3 months) Rheumatic heart disease CHADS₂ 5 or 6^e 	Bridging strongly recommended
Moderate risk	CHADS ₂ 3 or 4 ^e	Bridging should be considered
Low risk	CHADS ₂ score 0-2 ^e (and no prior stroke/TIA)	Bridging rarely necessary
^e CHADS ₂ score: Congestive heart failure/LV dysfunction (1), Hypertension (1), Age > 75 years (1), Diabetes Mellitus (1), previous Stroke/TIA (2)		
(3) VENOUS THROMBOEMBOLISM		
High risk	<ul style="list-style-type: none"> Recent (within 3 months) of VTE Severe thrombophilia^f 	Bridging strongly recommended ^g
Moderate risk	<ul style="list-style-type: none"> VTE within past 3 to 12 months Non-severe thrombophilic conditions Recurrent VTE Active cancer (Rx within 6 months or palliative) 	Bridging should be considered
Low risk	Single VTE more than 12 months and no other risk factors	Bridging rarely necessary
^f Deficiency of protein C or S or anti-thrombin, antiphospholipid antibodies, multiple abnormalities ^g Heterogenous factor V Leiden mutation, prothrombin gene mutation ^h For some individual patients the use of vena cava filter may need to be discussed.		
High risk: > 10% per year risk of arterial thromboembolism or > 10% per month risk of venous thromboembolism Moderate risk: 4-10% per year risk of arterial thromboembolism or 4-10% per month risk of venous thromboembolism Low risk: <4% per year risk of arterial thromboembolism or <4% per month risk of venous thromboembolism.		

17.2% in patients on continued aspirin, warfarin or both prior to sub-Tenon's anaesthesia, which was statistically significant compared to patients whose anti-thrombotic agents were discontinued for 1 week pre-operatively [20]. This is in contrast to patients on DAPT, who may have an increased risk of sight-threatening haemorrhagic complications. It is recommended either that elective ophthalmic procedures are postponed until it is safe for the patient to discontinue one of the antiplatelet agents during the peri-operative period or perform the surgery under less invasive anaesthetic routes, for example, under topical anaesthesia.

Cataract Surgery

Antiplatelet agents (Table 3), when used either as monotherapy or dual therapy, have not been associated with an increased risk of haemorrhagic complications. However, if surgery is carried out under peri- or retro-bulbar anaesthetic

block, it is recommended that the P2Y₁₂ receptor inhibitors are discontinued peri-operatively after the high-risk thromboembolic period [21]. This is due to haemorrhagic risks associated with the anaesthetic block rather than the cataract surgery itself.

Jamula et al. undertook a systematic review of the literature to study the incidence of haemorrhagic complications in patients continuing warfarin peri-operatively during cataract surgery [22]. They analysed 11 studies (4 cohort, 1 RCT and 6 case series) and reported increased risk of bleeding in patients taking warfarin (10%) with an odds ratio of 3.26 compared to non-anticoagulated patients undergoing surgery. However, most were self-limiting and non-significant events that included dot hyphaema and subconjunctival haemorrhages. They concluded that there was no evidence that continuation of warfarin was associated with sight-threatening haemorrhagic complications during cataract surgery [22]. The RCOphth recommends

Table 2 Incidences of haemorrhagic complications associated with local anaesthesia related to ophthalmic procedures

Local anaesthesia related to ophthalmic procedures								
Reference	Type of study	Number on anti-thrombotics	Type of anaesthesia	Type of surgery	Sub-conjunctival haemorrhage	Eyelid bruising/echymosis	Retro/peri-bulbar haemorrhage	Comment
[47]	Case report	On aspirin + prasugrel for a drug-eluting coronary stent inserted 4 months previously.	Retro-bulbar	Pan-retinal photocoagulation for PDR	-	-	Retrobulbar haemorrhage →NLP on discharge	Delay the procedure if DAPT required or hold prasugrel in the peri-operative period or use an alternate anaesthetic block.
[48]	Retrospective study	153 611 patients	Retro/peri-bulbar	Any	-	-	3/153 611 (all had poor visual outcomes)	Patient 1: aspirin + clopidogrel (also had a suprachoroidal haemorrhage) Patient 2: aspirin + clopidogrel + warfarin (INR 4.1) Patient 3: warfarin; delayed haemorrhage after a bout of coughing (two days post op admitted with acute bronchitis → switched to enoxaparin)
[3]	Prospective case-control study	Clopidogrel: 1000 Non-users: 1000	Peri-bulbar	Any – approx. 50% cataract surgery.	Grade 1 (spot echymosis of conjunctival haemorrhage) = 30/1000 (3.0%) in clopidogrel group and 20/1000 (2.0%) in non-users Grade 2 (eyelid echymosis involving half the lid) 0/1000 in both groups Grade 3 (eyelid echymosis all around the eye with no increase in IOP) = 0/1000 in both groups.		Grade 4 (retrobulbar haemorrhage + increased IOP) = 0/1000 in both groups	Clopidogrel not associated with sight-threatening complications due to peri-bulbar anaesthesia
[49]	Prospective case-control study	Aspirin: 500 (75–300 mg) Non-users: 500	Peri-bulbar	Any – approx. 50% cataract surgery	Grade 1 (spot echymosis): 30/500 (6.0%) in aspirin group and 20/500 (4.0%) in non-users Grade 2: 0/500 in aspirin group and 1/500 (0.2%) in non-users. Grade 3: 0/500 in both groups.		0/500	Peribulbar anaesthetic block can be safely performed in patients treated with aspirin.
[20]	Non-randomised case series 558 procedures (355 patients)	Continued warfarin/aspirin/both: 273 Discontinued warfarin/aspirin/both: 285 (One week pre-op and re-started 2 days post-op)	Sub-Tenon's	Cataract surgery	Continued: 47/273 (17.2%)* Discontinued: 31/285 (10.9%)	-		
[19]	48 862 operations on the Cataract National Dataset from 8 NHS Trusts 32 686/48 862	Aspirin: 9101 Clopidogrel: 524 Dipyridamole: 78 Aspirin + clopidogrel: 134 Aspirin + dipyridamole: 217 Warfarin: 1525 Aspirin + warfarin: 76 Non-users 21 001	Sub-Tenon's or sharp needle	Cataract surgery	Aspirin: 182/9101 (2.0%) Clopidogrel: 23/524 (4.4%)* Dipyridamole: 2/78 (2.6%) Aspirin + clopidogrel: 4/134 (3.0%) Aspirin + dipyridamole: 22/17 (0.9%) Warfarin: 56/1525 (3.7%)* Aspirin + warfarin: 5/76 (6.6%)* Non-user: 353/21 001 (1.7%)	Aspirin: 28/9101 (0.3%) Clopidogrel: 1/524 (0.2%) Dipyridamole: 0/78 Aspirin + clopidogrel: 1/134 (0.7%) Aspirin + dipyridamole: 0/217 (0.0%) Warfarin: 4/1525 (0.3%) Aspirin + warfarin: 1/76 (1.3%) Non-user: 44/21 001 (0.2%)	Aspirin: 4/9101 (0.04%) Clopidogrel: 0/524 Dipyridamole: 0/78 Aspirin + clopidogrel: 0/134 Aspirin + dipyridamole: 1/217 0.5%) Warfarin: 0/1525 Aspirin + warfarin: 0/76 Non-users: 7/ 21 001 (0.03%)	Haemorrhagic complications significantly associated with clopidogrel (8.0%) and warfarin (6.2%) compared to non-users (4.3%) but none sight-threatening. Unknown if anti-thrombotic agents were continued or discontinued peri-operatively.
[50]	Case report	Aspirin and clopidogrel	Sub-Tenon's	PPV for non-resolving VH (type 1 DM)			Retrobulbar haemorrhage	Post-op vision?

* Statistically significant results

Table 3 Incidences of haemorrhagic complications associated with cataract surgery

Cataract surgery					
Refer-ence	Type of study	Number on anti-thrombotics	Hyphaema	Vitreo-retinal haemorrhages	Suprachoroidal haemorrhage
[51]	Prospective non-randomised comparative study 60 eyes (60 patients)	Warfarin: 30 Mean INR 2.04 Non-user: 30	0/30 both groups	0/30 both groups	0/30 both groups
[52]	Prospective interventional case series 51 eyes (40 patients)	Warfarin + aspirin: 47 Warfarin + clopidogrel: 4 INR ≤ 3.0	0/51	0/51	0/51
[20]	Non-randomised case series 558 procedures (355 patients)	Continued warfarin/ aspirin/both: 273 Discontinued warfarin/ aspirin/both: 285 (One week pre-op and re-started 2 days post-op)	Continued: 8/273 (2.9%) Discontinued: 5/285 (1.8%) All microscopic hyphaema	Dot retinal haemorrhage Continued: 3/273 (1.1%) Discontinued: 2/285 (0.7%) No VH in either group.	Continued: 0/273 Discontinued: 0/285
[19]	48 862 operations on the Cataract National Dataset from 8 NHS Trusts	Aspirin: 13 110 Clopidogrel: 712 Dipyridamole: 128 Aspirin + clopidogrel: 190 Aspirin + dipyridamole: 317 Warfarin: 2372 Aspirin + warfarin: 94 Non-users: 31 901	Aspirin: 8/13 110 (0.06%) Clopidogrel: 1/712 (0.1%) Dipyridamole: 0/128 Aspirin + clopidogrel: 0/190 Aspirin + dipyridamole: 0/317 Warfarin: 2/2372 (0.08%) Aspirin + warfarin: 0/94 Non-users: 14/31 901 (0.04%)	-	Aspirin: 7/13 110 (0.5%) Clopidogrel: 2/712 (0.3%) Dipyridamole: 0/128 Aspirin + clopidogrel: 0/190 Aspirin + dipyridamole: 0/317 Warfarin: 1/2372 (0.04%) Aspirin + warfarin: 0/94 Non-users: 22/31 901 (0.7%)
[53]	Prospective, non-randomised, interventional, consecutive case series 75 eyes (63 patients)	Warfarin: all Plus antiplatelet: 9 patients Mean INR 2.03	1/75 microscopic hyphaema (1.3%)	1/75 dot retinal haemorrhage (1.3%)	2/75 iris haemorrhage (2.7%) All resolved spontaneously within one week. Mean INR of patients who had minor bleeding 2.1. No bleeding events recorded in patients treated with combined methods.

continuing warfarin during cataract surgery [23]. Their guidelines states surgery can be carried out if INR is within therapeutic range and consideration for sub-Tenon's or topical anaesthesia should be given in patients on warfarin to minimise the risk of haemorrhagic complications. Batra et al. recommended that the patients should be informed about the risks and benefits of continuing warfarin therapy during cataract surgery [24]. It has been shown that the risk of stroke increases to 1 in 100 with discontinuing warfarin and the risk of orbital haemorrhage increases by 0.2% to 1.0% if warfarin is continued and sharp needle local anaesthesia is performed [24].

To date no study has been designed to evaluate the risk of haemorrhagic complications during cataract surgery related to DOACs. Since DOACs provide more predictable anticoagulation with fixed dosing that is less prone to interaction with other medication compared to warfarin, they theoretically have a risk profile that is equal to or better than warfarin [25]. Therefore, Blum et al. recommended continuing DOACs during the peri-operative period in routine cataract surgery, although they did acknowledge the need for studies in the future to provide an evidence base for recommending guidelines [25]. In our proposed pathway, we suggest that DOACs are omitted 2 days pre-operatively (depending on renal function) and re-started 1 to 2 days post operatively if adequate haemostasis is achieved (Fig. 4 and Table 1).

Fig. 4 Proposed pathway for the peri-operative management of ophthalmic patients on anti-thrombotic agents

LOW RISK SURGERY			HIGH RISK SURGERY		
<ul style="list-style-type: none"> Sub-Tenon/topical cataract surgery Corneal surgery Oculoplastic: chalazion, eyelid cyst/lesion removal Strabismus 			<ul style="list-style-type: none"> Peri/retro-bulbar anaesthesia Glaucoma surgery Vitreo-retinal surgery (PPV) Vitreo-retinal surgery (oncology: endoresection, biopsy of intraocular tumours, plaques/markers) Oculoplastics: blepharoplasty, post-septal eyelid surgery Temporal artery biopsy 		
ANTIPLATELETS	ANTICOAGULANTS		ANTIPLATELETS	ANTICOAGULANTS	
	Warfarin	DOACs		Warfarin	DOACs
Continue.	Check INR on day of surgery and continue if within therapeutic range.	Omit dose 2 days pre-operatively (depends on renal function) and re-start 1-2 days post operatively if adequate haemostasis achieved.	Aspirin/clopidogrel: stop 7 days pre-operatively, continue in high risk. Prasugrel: stop 7 days pre-operatively* Ticagrelor: stop 5 days pre-operatively*	Inform the local anti-coagulant service at time of listing. If low risk (e.g. non-valvular atrial fibrillation): stop 2 days pre-operatively, check INR on day of surgery, and continue if <2. Re-start on evening of surgery. If high risk: discuss with physician.	Omit dose 2 days pre-operatively (depends on renal function) and re-start 1-2 days post operatively if adequate haemostasis achieved.
*only stop if after high thrombosis risk period or liaise with cardiologist if uncertain >12 months after insertion of drug-eluting coronary stent >1 month after insertion of bare metal coronary stent					

Glaucoma Surgery

Alwitry et al. (Table 4) collected data from a questionnaire that was sent to glaucoma specialists in England [13]. They reported that approximately 31% of the surgeons discontinued aspirin and 33% discontinued warfarin, of which 14% routinely started heparin and 38% started heparin depending on the indication for anticoagulation. Most surgeons (81.25%) proceeded with surgery if the INR was three or less, whereas 18.75% operated at higher INR. Interestingly, a similar study done in Brazil, reported that 82.7% of glaucoma surgeons stopped aspirin and warfarin [26].

Studies have shown an increased risk of haemorrhagic complications with anti-thrombotic use in glaucoma surgery. One study showed that aspirin use is associated with an increased incidence of hyphaema (50.9%) compared to anti-thrombotic non-users (28.0%), however, this did not affect the surgical outcome at 2 years [27]. In this study, the five patients who were on warfarin, all had significant hyphaema that lead to trabeculectomy failure in four of the five patients. The authors recommended continuing aspirin but discontinuing warfarin peri-operatively during glaucoma surgery. Multivariate analysis has shown that anticoagulant use and high pre- and post-operative intraocular pressures (IOP) to be risk factors for haemorrhagic complications [28]. Kojima et al. reported the incidence of

Table 4 Incidences of haemorrhagic complications associated with glaucoma surgery

Glaucoma surgery							
Refer- ence	Type of study	Number on anti- thrombotics	Type of surgery	Hyphaema	Vitreo-retinal haemorrhages	Suprachoroidal haemorrhage	Comment
[28]	Retrospective case-control study 694 eyes	Antiplatelet: 247 continued and 52 discontinued 2 weeks pre-op. Anticoagulant: 21 continued vs. 19 discontinued (2– 3 days pre-op). Both: 1 continued and 7 discontinued (antiplatelet 2 weeks and anticoagulant 2– 3 days pre-op). Non-users: 347	Trabeculectomy ± cataract surgery	Antiplatelet Continued: 5/247 (2.0%) Discontinued: 3/ 52 (5.8%) Anticoagulant Continued: 3/21 (14.3%) Discontinued: 1/ 19 (5.3%) Both Continued: 0/1 Discontinued: 1/7 (14.3%)	Antiplatelet Continued: 4/247 (1.6%) Discontinued: 2/ 52 (3.8%) Anticoagulant Continued: 2/21 (9.5%) Discontinued: 1/ 19 (5.3%) Both Continued: 0/1 Discontinued: 0/1	Antiplatelet Continued: 8/247 (3.2%) Discontinued: 2/52 (3.8%) Anticoagulant Continued: 2/21 (9.5%) Discontinued: 1/19 (5.3%) Both Continued: 0/1 Discontinued: 0/1	Antiplatelet Continued vs. discontinued 17/247 (6.9%) vs. 7/52 (13.5%), $p = 0.062$ Anticoagulant/both Continued vs. discontinued 7/22 (31.8%) vs. 4/26 (15.4%), $p = 0.113$ Overall: antiplatelet use (24/299, 8.0%) and anticoagulant use (± antiplatelet) (11/48, 22.9%) associated with a significantly higher incidence of haemorrhagic complications than non-users (13/347, 3.7%). Patients on anti-thrombotic agents who had a haemorrhagic complication had a significantly higher rate of severe vision loss compared to the non-users who had haemorrhagic complications (17.1% vs. 5.9%) NOTE: two of the patients in the anticoagulant use were on bridging subcutaneous heparin. Multivariate analysis: anticoagulant use and high pre-/post-op IOP were risk factors for haemorrhagic complications. Three thromboembolic events: 1 – antiplatelet discontinued pre-op →cerebrovascular accident 2 – antiplatelet continued → sixth nerve palsy 3 – non-user → pulmonary embolism
			Tube shunt procedure				
[27]	Retrospective 367 procedures	Aspirin: 55 Warfarin: 5 Non-users: 307	Trabeculectomy (6, 1.6% intra-operative anti- metabolites)	Aspirin: 28/55 (50.9%)* Warfarin 5/5 (100%)* Non-users: 86/307 (28.0%)	-	Aspirin: 1 (1.8%) Non-user: 1 (0.3%) Both resolved spontaneously.	

* Statistically significant results

hyphaema to be 24.8% in a Japanese population of patients undergoing trabeculectomy with mitomycin C [29]. They showed that neovascular glaucoma and antiplatelet and anticoagulant use are associated with an increased risk of hyphaema (OR: 2.4, $p = 0.0017$ and OR: 2.1, $p = 0.0274$, respectively). Of the patients with neovascular glaucoma, the risk is further increased with antiplatelet and anticoagulant use (OR 3.3, $p = 0.0450$). Pre-operative use of intravitreal anti-vascular endothelial growth factor (VEGF) injections was associated with a reduced risk in these patients (OR 0.36, $p = 0.0275$) [29].

Golan et al. undertook a prospective controlled study in patients suspected of bilateral primary angle-closure glaucoma who were on antiplatelet or anticoagulant agents undergoing laser peripheral iridotomy [30]. They included 104 patients (204 eyes) of which, 49% were on aspirin, 32.7% were on warfarin and 18.3% were on clopidogrel. One eye had the procedure while on anti-thrombotic agents, whereas these agents were discontinued for 2 weeks prior to having the procedure in the second eye. The incidences of hyphaema in both eyes were 34.6% (36/104), which was not statistically significant irrespective of the anti-thrombotic agent used. The incidence of hyphaema when anti-thrombotic agents were continued were 31.4% for patients on aspirin, 41.2% for warfarin and 31.6% for clopidogrel. All the hyphaemas were either grade 1 (minor bleeding stopped by light pressure with Abraham contact lens) or 2 (bleeding not controlled with contact lens and no macroscopic hyphaema) [30].

Therefore, the recommendations in the literature are to discontinue aspirin and clopidogrel when used as monotherapy for primary prevention, however, continue if used for secondary prevention of cardiovascular diseases. The P2Y₁₂ receptor inhibitors should be discontinued if used as DAPT. However, risks and benefits of continuing antiplatelet agents should be considered in the presence of neovascular glaucoma and high IOPs. It is also important to consider and recognise that, intraoperative and post-operative haemorrhagic complications in glaucoma, especially if sustained or prolonged, can cause severe visual loss due to high pressure in already compromised optic nerves. Anticoagulants should be discontinued with consideration for bridging therapy depending on patient's risk factors.

Vitreo-Retinal Surgery

A recent survey that included 167 (Table 5) members of the British and Eire Association of Vitreoretinal Surgeons showed that 93% and 82% of the respondents continued aspirin and clopidogrel peri-operatively, respectively [7]. Moreover, 79% of the respondents reported to continuing warfarin and 58% continued DOACs peri-operatively. More than 90% of the surgeons would continue with surgery if

the INR is between 1.0 and 3.0, 43% if INR between 3.0 and 3.5 and only 7% would continue with surgery if INR is more than 3.5. In this survey, only 9% of the surgeons reported to stopping all anticoagulant agents during diabetic vitrectomy and retinectomy [7].

The incidence of post-operative vitreous haemorrhage following vitrectomy for complications of proliferative diabetic retinopathy (PDR) is reported to be between 20 and 30% [7]. Patel et al. carried out cumulative data analysis of studies, who reported incidence rates of haemorrhagic complications to be 17.5% (36 of 206 eyes) with aspirin, 7.4% (15 of 204 eyes) with clopidogrel, 16.7% (7 of 42 eyes) with dual therapy with aspirin and clopidogrel, 13% (3 of 23 eyes) with prasugrel, 8.3% (22 of 266 eyes) with warfarin and 7.7% (1 of 13 eyes) with DOACs [7].

Chandra et al. undertook a prospective study on 5459 patients that underwent pars plana vitrectomy over a ten year period and looked at the incidence of suprachoroidal haemorrhages [31]. Suprachoroidal haemorrhages were observed in 56 patients (1.03%) during the study period. Multivariable logistic regression showed use of aspirin and warfarin (OR 2.29, $p = 0.007$) to be risk factors for developing suprachoroidal haemorrhages [31]. Another study by Brillat et al. reported that aspirin continued or discontinued for 5 days or less peri-operatively was not associated with an increased risk of haemorrhagic complications during retinal detachment surgery [32]. In contrast, a retrospective study by Ryan et al. did not show anti-thrombotic agents to be a risk factor for intra and post-operative haemorrhagic complications [33]. Similarly, another study by Brown et al. concluded that there was no increased risk of post-operative dense vitreous haemorrhages in patients undergoing diabetic vitrectomy between patients on aspirin, clopidogrel or warfarin compared to those who discontinued these medication peri-operatively or non-users [34]. However, studies have shown PDR (OR 4.1, $p = 0.003$) and diabetes (OR 18.5, $p < 0.001$) to be risk factors for intra and post-operative haemorrhagic complications, respectively [33]. Use of anti-VEGF injections to reduce post-operative recurrent vitreous haemorrhages is becoming popular in patients with PDR [33, 35]. Fabinyi et al. reported that diabetic patients undergoing PPV while on anti-thrombotic agents (aspirin/clopidogrel/warfarin) peri-operatively are more likely to have persistent vitreous haemorrhage (OR 4.8, $p = 0.004$) and subsequent surgery (OR 6.6, $p = 0.024$) [35]. Oh et al. reported glaucoma also be a risk factor associated with haemorrhagic complications following vitreoretinal surgery [1].

Due to controversial results from studies, the recommendations for peri-operative management is similar to that for glaucoma surgery. Anti-thrombotic agents are to be discontinued where possible and to be cautious of these agents in the presence of neovascular retinal diseases.

Table 5 Incidences of haemorrhagic complications associated with vitreoretinal surgery

Vitreoretinal Surgery							
Reference	Type of study	Number on anti-thrombotics	Type of surgery	Vitreous haemorrhage	Sub-retinal haemorrhage	Suprachoroidal haemorrhage	Comment
[54]	Retrospective consecutive series review of patients on rivaroxaban, apixaban, dabigatran, and prasugrel 108 eyes	Prasugrel: 23 Dabigatran: 6 Rivaroxaban: 5 Apixaban: 2 Non-users: 72	PPV ± scleral buckling	Prasugrel: 3/23 (13.0%) Rivaroxaban: 1/5 (20%) Control: 6/72 (8.3%); 4 required further surgical interventions	Anti-thrombotic: 0/36 Control group: 0/72	Anti-thrombotic: 0/36 Control group: 0/72	No incidence of retrolbulbar haemorrhages in either group. No significant difference between the control group and patients on anti-thrombotic agents (4/36, 11.1%) Of the 4 patients who had VH while on anti-thrombotic agents, 3 underwent PPV for VH secondary to PDR (2 required further surgery) and 1 underwent PPV for RD. Not reported the type of anti-thrombotic agent associated with type of haemorrhagic complication. No control group.
[33]	Prospective study 107 surgeries	Aspirin: 77 Clopidogrel: 8 Aspirin + clopidogrel: 11 Warfarin: 11 (Mean INR 2.4)	95 PPV 12 scleral buckling	Hyphaema 6/107 (5.6%) Mild-moderate VH: 32/107 (29.9%) Dense VH 6/107 (5.6%) Sub-retinal haemorrhage 2/107 (1.9%) Suprachoroidal haemorrhage 3/107 (2.8%) (None sight-threatening) Haemorrhagic events: Aspirin: 38/77 (49.4%) Clopidogrel: 1/8 (12.5%) Aspirin + clopidogrel: 7/11 (63.6%) Warfarin: 3/11 (27.3%)	Retinal haemorrhage/haematoma Antiplatelet: 3/44 (6.8%)* Anticoagulant: 0/12 Control: 4/144 (2.8%)		Sub-conjunctival haemorrhage and hyphaema: Antiplatelet: 1/44 (2.3%) Anticoagulant: 2/12 (16.7%) Control: 7/144 (4.9%) 3 sight-threatening complications: all reported in patients using clopidogrel (two wet AMD and one DR). Antiplatelet agents had a significantly higher incidence of severe haemorrhagic complications (VH and retinal haemorrhage/haematoma) than patients in anticoagulants and control group. Continue antiplatelet agents peri-operatively in diabetic vitrectomy. No report of incidence of haemorrhagic complications
[4]	Retrospective case series 200 eyes	Aspirin/clopidogrel/both: 44 Anticoagulants: 12 (target INR < 4.5) Control: 144	PPV ± cataract surgery	Antiplatelet: 6/44 (13.6%)* Anticoagulant: 0/12 Control: 3/144 (2.1%)			
[34]	Retrospective comparative cohort study 97 eyes	Continued (27): 16 aspirin, 1 clopidogrel 10 aspirin + clopidogrel	Diabetic PPV (single surgeon)	Dense VH: Anti-platelet: 3/27 (11.1%); 1 required further surgery.	-	-	

Table 5 (continued)

Vitreoretinal Surgery			
	Control group: discontinued anti-thrombotics and non-users (70)		associated with each anti-thrombotic agent. No report of incidence of haemorrhagic complications in patients who discontinued medication compared to non-users. Patients who continued anti-thrombotic agents peri-operatively had significantly higher incidence of VH (8/29, 27.6%) compared to the non-users (6/87, 6.9%). Diabetic patients undergoing PPV while on anti-thrombotic agents peri-operatively are more likely to have persistent vitreous haemorrhage (OR 4.8, $p = 0.004$) and subsequent surgery (OR 6.6, $p = 0.024$).
[35]	Retrospective chart review 155 eyes	Control: 12/70 (17.1%); 4 required further surgery. Anti-thrombotic agents (68): 29 continued 39 discontinued peri-op Non-users: 87 Diabetic PPV 5/18 aspirin (27.8%); 3 required further surgery. 1/4 clopidogrel (25%) required further surgery. 2/2 warfarin (100%); no further surgery. Discontinued: 4/39 (10.3%); 3 required further surgery. Non-users: 6/87 (6.9%); none required further surgery.	-
[55]	Retrospective case-control study 120 patients	Warfarin: 60 (INR 0.94–4.6, median 2.3) Non-users: 60 PPV	Warfarin: 0/60 Control: 1/60 (1.7%)
[56]	Retrospective cohort study 310 procedures	(Procedures) Warfarin: 64 Clopidogrel: 136 Control: 110 25 gauge PPV	Warfarin: 1/64 (1.6%) Clopidogrel: 5/136 (3.7%) Control: 4/110 (3.6%) 0 in all groups.
[1]	Observational retrospective case-control study 822 patients	Aspirin: 168 Clopidogrel 25 Both 21 (145 discontinued 3 days pre-op) Warfarin 25 (18 discontinued for less than 5 days) PPV 740 Scleral buckling 82 One surgeon	Hyphaema 17/822 (2.1%) VH: 66/822 (8.0%) Sub-retinal haemorrhage 4/822 (0.5%) Suprachoroidal haemorrhage 6/822 (0.7%) Continued antiplatelet: 12/69 (17.4%) Discontinued antiplatelet: 14/145 (9.7%) Anticoagulant: 7/25 (28%)* Non-users: 61/588 (10.4%)

* Statistically significant results

Oculoplastic And Lacrimal Surgery

In general, eyelid procedures anterior to the orbital septum (Table 6) (chalazion and eyelid lesion removal) are associated with low risk of sight-threatening haemorrhagic complications, whereas eyelid procedures posterior to the septum (ptosis surgery and lower lid blepharoplasty) and deep orbital surgery are associated with potentially sight-threatening haemorrhagic complications [5, 6]. Lacrimal surgery, such as dacrocystorhinostomy, is also associated with a moderate risk of epistaxis are also classed as a high-risk procedure [5, 6]. There are sparse studies done to investigate the risk of haemorrhagic complications in patients on anti-thrombotic agents undergoing oculoplastic and lacrimal surgery. Expert groups on oculoplastic surgery recommend stopping anti-thrombotic agents during blepharoplasty, lacrimal surgery and deep orbital surgery as these are considered high risk for sight-threatening haemorrhagic complications [5].

There were only two retrospective chart review studies found during our literature review on patients undergoing oculoplastic and lacrimal surgery. One study showed a significantly higher incidence of intra-operative haemorrhage during high-risk oculoplastic procedures in patients who discontinued anti-thrombotic agents pre-operatively compared to non-users, however, there was no significant difference in the incidence of haemorrhagic complications in patients who continued their anti-thrombotic medication peri-operatively and non-users [36]. The second study included patients who had patients that discontinued their anti-thrombotic medication pre-dacrocystorhinostomy and reported no increased risk of delayed epistaxis in these patients compared to non-users [37].

To date there are no studies investigating the safety of continuing DOACs peri-operatively in patients undergoing oculoplastic and lacrimal surgery. However, due to the better safety profile of DOACs compared to warfarin, it may be advisable to follow the same recommendations made for warfarin with DOACs [6]. Liu et al. presented two case reports of patients on rivaroxaban who had haemorrhagic complications after uncomplicated eyelid surgery [38]. Patient 1 had bilateral upper blepharoplasty who stopped rivaroxaban 24 h pre-operatively, however, despite medical advice re-started medication the evening of the surgery. He presented with left eye orbital compartment syndrome. Following decompression, the post op vision was 20/20. The second patient had bilateral ectropion repair who was on rivaroxaban that was stopped 24 h pre-operatively and re-started medication 8 h post-operatively. Within 2 h of re-starting rivaroxaban patient presented with left lower eyelid bleeding that stopped with electrocautery and Surgicel with no sequelae [38].

Table 6 Incidences of haemorrhagic complications associated with oculoplastic and lacrimal surgery

Reference	Type of study	Number on anti-thrombotics	Type of surgery	Haemorrhagic complications	Comment
[36]	Retrospective chart review 1130 surgeries in 1015 patients	448/1130 (39.6%) on anti-thrombotic agents. Mean INR 1.47 (1.06–2.84)	Minor oculoplastic procedures excluded but not stated what was included precisely.	Continued group (145): 1 post-op haemorrhage (aspirin but stopped clopidogrel 5 days pre-op and re-started day 1 post-op) – not stated type of surgery Discontinued group (207): 3 intra-op (DCR – stopped aspirin 5 days pre-op; excision of an orbital AV malformation – stopped aspirin more than 7 days pre-op; cicatricial ectropion repair – stopped warfarin 3 days pre-op, INR 1.3) and 1 post-op haemorrhage (lower blepharoplasty – stopped aspirin 3 weeks pre-op) (1.9%) Non-users (682): 1 post-op orbital haematoma (lymphangioma debulking) (0.14%)	Significant difference in incidence of intra-op bleeding between the discontinued group and non-users. None sustained permanent visual deficit or deformity related to haemorrhage.
[37]	Retrospective chart review 437 surgeries in 374 patients	79 on aspirin, 37 NSAIDs and 7 on warfarin. Aspirin stopped 2 weeks, NSAIDs 1 week and warfarin 5 days (target INR < 1.5) pre-operatively	External DCR (one surgeon)	Delayed epistaxis (2–8 days post-operatively) 15/437 (3.4%) – not reported how many of these were on anti-thrombotic agents.	Older age (likely due to poor wound healing response) and history of dacrocystitis were risk factors for delayed epistaxis. Use of anti-thrombotic agents not found to increase the risk of delayed epistaxis.

Due to the rapid onset of action of DOACs, it is recommended not to re-start these medications too soon after high-risk procedures [6].

In patients undergoing high-risk procedures who are also at high risk of thromboembolic events and are unable to discontinue their regular medication, it is recommended to discuss with patients regarding alternate or less invasive treatments or to alter the surgical technique if possible to reduce haemorrhage [6]. If it is essential to discontinue anti-thrombotic agents, it is advised that a discussion with the cardiology team is made [5].

Strabismus Surgery

There was only one study that reported the incidence of haemorrhagic (Table 7) complications associated with anti-thrombotic agents in patients undergoing strabismus surgery. Kemp et al. retrospectively identified three patients who continued warfarin out of 155 patients that underwent strabismus surgery [39]. They reported that all three patients had INR within the therapeutic range of 2.0 to 3.0 and none had haemorrhagic complications. However, they did not report on patients who were on antiplatelet agents and their associated risk of haemorrhagic complications. Recommendations in the literature for the peri-operative management of anti-thrombotic agents are similar to glaucoma and vitreoretinal surgery.

Corneal Surgery

Haemorrhage-related complications are rare but well recognised in corneal surgery due to the devastating consequence of vision loss. The incidence of suprachoroidal haemorrhages in penetrating keratoplasty (PKP) have been reported to be 0.73% [40]. In 'open sky' scenarios, eyes are at an increased risk of an expulsive choroidal haemorrhage due to sudden globe decompression. Park et al. reported the incidence of vitreous haemorrhage in PKPs as 0.75% [41]. Delayed suprachoroidal haemorrhages have been reported after Descemet stripping automated endothelial keratoplasty (DSAEK) [42, 43].

Whilst there has been an association of spontaneous suprachoroidal haemorrhage with the use of systemic anticoagulants or thrombolytic agents in the absence of surgery or trauma [44, 45], we did not identify any studies published that evaluated the use of anti-thrombotic agents in corneal surgery. Crews et al. found that the pre-operative use of anticoagulant and antiplatelet medications did not increase the risk of hyphaema from the intraoperative peripheral iridotomy in Descemet membrane endothelial keratoplasty (DMEK) [46].

Expert opinion recommends antiplatelet monotherapy to be continued and second agent to be discontinued if

Table 7 Incidences of haemorrhagic complications associated with strabismus surgery

Strabismus surgery			
Reference	Type of study	Number on anti-thrombotics	Haemorrhagic complications
[39]	Retrospective chart review 155 patients	3 on warfarin	0/3 Patient 1: warfarin stopped 1 day pre-op and re-started soon after surgery (INR 2.3) Patient 2: warfarin continued; INR between 2 and 3 Patient 3: warfarin continued; INR 2.0
			Comment No report on use of antiplatelet agents and incidence of haemorrhagic complications.

dual therapy is used during keratoplasty and surgery for pterygium [21]. They recommend warfarin to be continued if INR is within therapeutic range and DOACs to be discontinued if after the high thrombotic risk period due to the lack of evidence on DOACs [21].

Our Recommendations

Our recommendations made following the literature review and advice from our local ophthalmology consultants are shown in Fig. 4.

Conclusions

Most studies in the literature are retrospective and are not of the highest quality of evidence, such as RCTs. Moreover, the incidences of haemorrhagic complications are rare limiting the statistical power of studies.

In any case it is important to consider the indication for anti-thrombotic agents and the risk of thromboembolic events, as well as risk of haemorrhagic complications depending on patient and surgical factors. Bridging anticoagulation should be considered when oral anticoagulant agents are discontinued. The most appropriate surgical procedure should be offered to the patient depending on the risk of haemorrhage peri-operatively when anti-thrombotic agents are continued. When urgent surgery is required or when a patient's case is complex, it is important to take a multidisciplinary approach to the peri-operative management of anti-thrombotic agents.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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