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PREOPERATIVE MANAGEMENT OF PATIENTS ON CHRONIC ANTITHROMBOTIC THERAPY WHO REQUIRE ELECTIVE NON-CARDIAC SURGERY

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Preoperative management of antithrombotic therapy (antiplatelet and anticoagulant therapy) is challenging since discontinuation of therapy carries a risk of the thromboembolic event and surgery carries a risk of bleeding. An optimal balance between thromboembolic and bleeding risk must be reached and the decision whether to stop antithrombotic therapy or not be made. Each patient requires an individual assessment. That means estimating bleeding and thromboembolic risk for each patient. Bleeding risk is based on patient-related risk factors and risk associated with the surgical procedure. Thromboembolic risk is more complex to calculate. If the decision is to stop antithrombotic therapy, the next question is how long before the surgery it should be stopped and whether the bridging therapy is required.

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Introduction

Antithrombotic (AT) therapy is used to minimize the incidence of arterial and/or venous thrombosis in patients at increased risk. At increased risk are patients with atrial fibrillation (AF), mechanical heart valves (MHV), recent arterial or venous thromboembolism (VTE), patients with implanted stents (1). The most widely used AT drugs are antiplatelet (AP) drugs like acetylsalicylic acid (ASA) and P2Y12 inhibitors and anticoagulant (AC) drugs like vitamin K antagonists (VKA) and direct oral anticoagulants (DOAC) (2). A lot of patients on AT therapy will need surgery and preoperative management is very complex. If therapy is stopped, the risk of thrombosis during and after surgery is increased. Not stopping the therapy increases the risk of bleeding. The balance between thromboembolic (TE) risk and bleeding (BL) risk has to be made. In order to make this balance we need to estimate the individual's risk of thrombosis, the individual's risk of bleeding and the risk of bleeding that surgery carries. If the decision is to stop AT therapy, the next question is the timing of interruption and using of bridging therapy (3-5). We will answer these questions in our paper.

Thromboembolic risk in patients on anticoagulant therapy

There are three main conditions associated with increased risk of thromboembolism: AF, MHV and recent VTE.

Atrial fibrillation

The most common reason of preoperative AC use is AF. Six million patients with AF require surgery each year (6). The TE risk in these patients is estimated by CHA2DS2VASc score (Table 1). This score is based on the presence of congestive heart failure, hypertension, patient's age, diabetes mellitus, history of stroke/TIA, vascular disease and sex. The highest score is 9 points and a total score of 2-3 points means low TE risk (< 5%), 4-5 points moderate TE risk (5-10%) and a score over 6 points high TE risk (< 10%) (Table 2) (7-9).

Mechanical heart valves

TE risk in patients with MHV without AC therapy is 8-22% (9). The use of warfarin reduces this

risk by 80% (10). The INR in patients with aortic MHV without other TE risk factors should be 2.5, while in those with associated TE risk factors or mitral MHV the INR should be 3.0. Additional risk factors include AF, ejection fraction (EF) lower than 40%, older age, hypercoagulable state and previous TE. The location, type and number of MHV are important indicator of TE risk. The highest risk is with multiple MHV, followed by mitral MHV and lowest with aortic MHV (Table 2) (11).

Recent thromboembolism

The greatest risk is immediately after TE event and decreases over time. Therefore, surgery should be delayed for three months, if possible. Recurrence of VTE is greatest in 3-4 weeks after initial event and decreases in the next three months. Without AC therapy the probability of recurrent VTE is 50%. Warfarin therapy reduces this risk to 8-10% after one month of therapy and to only 4-5% after 3 months (12). If urgent surgery is needed, bridging therapy can be used to reduce the TE risk. The greatest risk is in patients with VTE or pulmonary thromboembolism (PTE) in last 3 months and in those with VTE associated with congenital thrombophilia. A TE event that occurred more than a year ago means low TE risk and the presence of malignancy moderate (Table2) (13, 14).

Table 1. CHA2DS2VAS score

Letter	Risk factor	Score
C	Congestive heart failure (EF < 40%)	1
H	Hypertension	1
A2	Age ≥ 75	2
D	Diabetes mellitus	1
S2	Stroke/TIA	2
V	Vascular disease	1
A	Age 65-74	1
S	Sex category (female)	1
	Maximum score	**9**

Table 2. Thromboembolic risk by anticoagulation indication

Risk	Atrial fibrillation	Mechanical valves	Venous thromboembolism (VTE)
Low (annual risk of VTE < 5%)	CHA2DS2VASc score 2-3	Bileaflet aortic valve without additional risk factors	VTE more than 12 months ago without additional risk factors
Moderate (annual risk of VTE 5-10%)	CHA2DS2VASc score 4-5 Stroke, TIA more than 3 months ago	Bileaflet aortic MHV and one or more additional risk factors: age>75, congestive heart failure, AF, previous stroke/TIA	VTE within 3-12 months Recurrent VTE active cancer non severe thrombophilia
High (annual risk of VTE > 10%	CHA2DS2VASc score > 6 Stroke, TIA in the last 3 months	Mitral Aortic (cage ball or tilting disk) Stroke, TIA in the last 6 months	VTE in the last 3 months severe thrombophilia

Thromboembolic risk in patients on antiplatelet therapy

The most common indication for AP therapy is the prevention of development and recurrence of arterial ischaemic events, including coronary artery disease (CAD), cerebrovascular events and peripheral arterial disease (15). Patients with CAD often undergo percutaneous coronary intervention (PCI) with stent implantation.

In North America, 5% of patients undergo non-cardiac intervention within 1 year of stenting (16). The period between the TE event and the surgery is the most substantial in estimating TE risk in patients on dual antiplatelet therapy (DAPT). The studies show that the greatest risk of TE event is present in patients who have surgery within 6 months of stent implantation (17). The next important factor is the type of stent. PCI with first generation Drug Eluting Stents (DES) has a higher incidence of thrombosis than those with Bare Metal Stents (BMS). Second-generation DES provide greater safety and lower incidence of thrombosis compared to BMS. Although experience with bio-

resorbable stents is limited, some research has shown an increased incidence of stent thrombosis. It is recommended that DAPT lasts at least 12 months for these stents. Since there is no risk of stent thrombosis, patients undergoing coronary artery bypass grafting (CABG) or non-invasive drug treatment are at lower risk of complications. The next important determinant is whether the disease is stable or not. Individuals with stable coronary artery disease have shown to be at a lower TE risk than those with acute coronary syndrome (ACS). Patient's comorbidities must also be considered. Patients who have had complex PCI also have a higher risk of thrombosis. Intervention in people who have had a stroke is also a risk factor, especially in the first 30 days after a stroke. Stent thrombosis in peripheral arterial disease is most common in the first month. The risk is highest in DES or stents in chronic occlusion. In patients with stent implantation in the lower extremities, the use of DAPT for at least 1 month has been suggested in the guidelines (Table 3) (14, 18-20).

Table 3. Thromboembolic risk by antiplatelet indication

Indication for antiplatelet therapy					
Risk	**Time on therapy (months)**	**ACS**	**Stable coronary artery disease**	**Cerebro-vascular disease**	**Peripheral artery disease**
High	< 3	Medical treatment	PCI + BMS/DES/DEB or CABG	Stroke, carotid stent placement	Acute TE on peripheral blood vessels + revascularisation or chronic occlusion
	< 6	PCI + BMS/DES/DEB or CABG	PCI + BMS/DES/DEB or CABG + risk factors		
	< 12	PCI + BMS/DES/DEB or CABG + risk factors PCI + first generation DES BVS	PCI + first generation DES BVS		
Moderate	3-6	Medical treatment	PCI + BMS/DES/DEB or CABG	Stroke, carotid stent placement	Acute TE on periphery blood vessels + revascularisation or chronic occlusion
	6-12	PCI + BMS/DES/DEB or CABG	PCI + BMS/DES/DEB DEB or CABG + risk factors		
	> 12	PCI + BMS/DES/DEB or CABG + risk factors PCI + first generation DES BVS	PCI + first generation DES BVS		
Low	> 6	Medical treatment	PCI + BMS/DES/DEB or CABG	Stroke, carotid stent placement	Acute TE on periphery blood vessels + revascularisation or chronic occlusion
	> 12	PCI + BMS/DES/DEB or CABG	PCI + BMS/DES/ or CABG + risk factors		

Bleeding risk

The most important factors in estimating the BL risk include the type of surgery and the clinical characteristics of the patient. These characteristics are determined by using the HAS-BLED bleeding risk score (H–hypertension, A–abnormal renal/liver function, S–stroke, B–bleeding tendency, L–labile INR, E–elderly, D–drugs or alcohol use) (Table 4). The score assigns 1 point for each of the risk factors and a HAS-BLED score greater than 3 points indicates an increased BL risk. The BL risk is divided into low (0-2% two-day risk of bleeding after surgery) and high risk (2-4% two-day risk of bleeding after surgery) (21). Examples of high BL risk interventions include major intraabdominal, major orthopedic, cardiac surgery, lung resection surgery, extensive cancer surgery, major urologic and vascular surgery. Examples of low BL risk interventions are cataract surgery, dental extraction surgery, skin biopsy, gastroscopy or colonoscopy without biopsy, carpal tunnel repair. Surgical interventions involving neuraxial, intracranial and cardiac sites are of special interest because of the anatomical localization of the source of hemorrhage (Table 5) (22).

Table 4. HAS-BLED score

Risk factor	Score
Hypertension	1
Abnormal renal/liver function	1 or 2
Stroke	1
Bleeding tendency	1
Labile INR	1
Elderly (age > 65)	1
Drugs (like aspirin, NSAIL), alcohol	1 or 2
Maximum score	9

Table 5. Bleeding risk according to procedure

High bleeding risk interventions	Low bleeding risk interventions
Major intracranial or neuraxial surgery	Gastrointestinal procedures (colonoscopy, gastroscopy, sigmoidoscopy, ERPC)
Major thoracic surgery (lobectomy, pneumonectomy, esophagectomy	Cardiac procedures (PCI, internal cardiac defibrillator implantation, coronary artery angiography
Major cardiac surgery	Dental procedures
Major vascular surgery (aortic aneurysm repair, aortobifemoral bypass, popliteal bypass)	Skin interventions (skin biopsy)
Major abdominal/pelvic surgery (hepatobiliary cancer resection, pancreatic cancer, colorectal and gastric cancer resection, bladder cancer resection, endometrial and ovarian cancer resection)	Eye interventions (cataract)
Major orthopedic surgery (hip arthroplasty, knee arthroplasty, shoulder arthroplasty)	
Other major cancer or reconstructive surgery	
Any surgery requiring neuraxial anesthesia	

Interrupt anticoagulant therapy or not?

An optimal balance between TE and BL risk must be made. Clinical assessment is imperative. Individuals at high BL risk will benefit from discontinuation of AC therapy. On the contrary, the patients at high TE risk require bridging and a period without anticoagulants as short as possible. Those scheduled for low BL risk surgery very often do not have to stop AC therapy. Efforts should be made to keep the risk of both bleeding and thrombosis as low

as possible, regardless of the status of AC therapy (Figure 1) (6, 23).

Timing of anticoagulant interruption

Therapy should be discontinued within a time frame sufficient to withdraw the effect of the drug. For some drugs, such as VKA, laboratory tests are a reliable indicator of AC activity. However, for DOACs, such tests are not always available.

Warfarin

Stop 5 days before surgery (last dose on a day minus 6). PT/INR should be checked one day prior to surgery. If the INR is higher than 1.5, give a low dose of vitamin K (1-2 mg) and check the INR on the morning of surgery (23). It is especially important that the INR is within the reference values in high BL risk surgeries or if neuraxial anesthesia is given. The timing of warfarin interruption is based on its half-life (36-42 h) and on the period of time for PT/INR to return to normal (2-3 days to INR fall to 2; 4-6 to become normal). This time may be longer in patients with higher INR values and in the elderly. Half-lives of some other VKA are longer (8-11 h for acenocoumarol, 4-6 days for phenprocoumon, 3 days for fluindione). This discontinuation schedule leads to several days when the AC effect is subtherapeutic, which requires bridging in those with a high or very high risk of TE event. Preoperative bridging is reserved for patients at high TE risk (e.g., recent stroke, MHV, CHA2DS2-VASc score 5, 6, 7, 8) who require discontinuation of AC therapy. The bridging drug is given in a therapeutic dose 3 days before the operation (13, 24, 25).

Direct oral anticoagulant drugs

Due to rapid cessation and rapid onset of action, patients on DOAC will have a shorter period in which they are without AC protection. In case of procedures associated with low/moderate BL risk, DOAC should be discontinued a day before surgery and administered again one day following the surgical procedure. Total interruption time is two days. In case of procedures associated with high BL risk, DOAC should be discontinued two days before surgery and administered again two days following the surgery. Total interruption time is four days. In individuals on dabigartran with CrCl of 30-50 ml/min one additional day is required for low/moderate BL risk interventions and two additional days for high BL risk interventions (26). No dose adjustment is required for other DOACs (apixaban, rivaroxaban, edoxaban). Due to rapid cessation and rapid onset of action bridging is not necessary. It is recommended for ones at high risk of postoperative TE who require extended interruption of therapy (e.g. postoperative ileus after abdominal surgery) (Figure 1) (6, 13, 23).

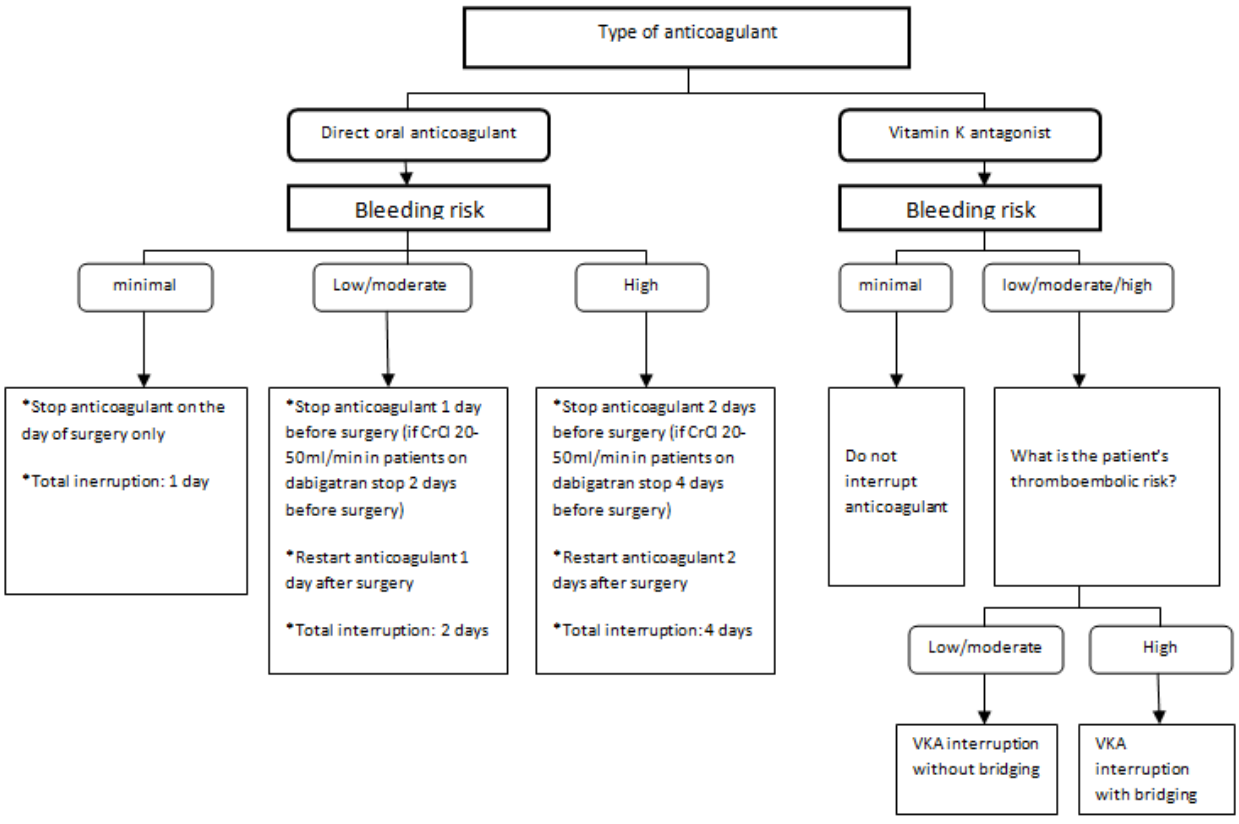

Figure 1. Algorithm for stopping anticoagulant therapy before surgery

Bridging in patients on anticoagulants

Bridging can be defined as the administration of a short-acting AT drug, most commonly a low molecular weight heparin (LMWH) or unfractionated heparin (UH) during the discontinuation period of a long-acting AT agent, most commonly warfarin. The purpose of bridging is to shorten the period during which AC coverage is absent and thus minimize the risk of perioperative TE event. However, a balance must be struck with the possibility of postoperative bleeding. Avoid bridging in patients with low TE risk like in routine prophylaxis in AF; in patients on DOACs, unless TE risk is high and postoperative period during which they cannot take DOACs is prolonged and in secondary prophylaxis of VTE which was more than 3 months ago. Bridging is advised when vitamin K antagonist is discontinued in the following cases: mitral MHV, aortic MHV with additional risk factors; stroke in the last three months or very high risk of stroke (CHADS2 score 5 or 6); VTE in the last 3 months; stent implantation in the last 3 months; previous TE during cessation of the therapy (12).

Heparin products and dosage

LMWH is most commonly used because of its equal efficacy as UH and greater reliability. Also, they generally do not require monitoring. UH is cheaper, its effects can be easily reversed and does not necessitate dose adjustment in renal insufficiency. The dose of LMWH can be prophylactic, therapeutic or moderate. Therapeutic dose is used in individuals with a source of possible embolus (AF, MHV) or VTE in the previous month. Therapeutic dose for enoxaparin is 1 mg/kg SC once a day and for dalteparin 100 IJ/kg SC twice a day. Moderate dose is used in patients with AF or VTE in the previous month when bridging is required but there is also BL risk. Moderate dose for enoxaparin is 40 mg SC twice a day and for dalteparin 5000 IJ SC twice a day. Dose adjustment is reserved for patients with renal insufficiency and obesity. In general, prophylactic doses are not used in individuals with AF, since there is no evidence that low doses are able to prevent stroke. It can be used in those with history of VTE in the last 3-12 months. The bridging therapy with LMWH starts 3 days before surgery (2 days after discontinuation of warfarin), when INR begins to fall below therapeutic values. LMWH should be stopped 24 h before surgery, based on the LMWH half-life which is 3-5 h. For twice-daily dosing, the last dose is given on the night before surgery and for once-daily dosing, one half of the last dose is given in the morning of the day before intervention. When therapeutic doses of UH are used, IV infusion is stopped 4-5 h before surgery, since the half-life of heparin is about 45 minutes. If subcutaneous UH is used, the most common dose is 250 IJ twice a day, with the last dose administered on the night prior to surgery (27-29).

Interrupt antiplatelet therapy or not?

The decision about stopping AP therapy should not be based only on the relationship between the risk of bleeding and thrombosis, but the indication for its use and the type of therapy should also be taken into consideration.

Antiplatelet monotherapy

ASA has to be stopped before surgery in patients on aspirin for primary prevention. If it is prescribed for secondary prevention, it should not be stopped (an exception involves patients at very high BL risk and in that situation, it has to be stopped for 7-10 days prior to surgery) (30). Monotherapy with some of P2Y12 inhibitors can be replaced with ASA if a patient requires surgery with moderate BL risk. If AP monotherapy is stopped, it should be restarted in the shortest possible time.

Dual antiplatelet therapy

After coronary artery stent placement, 4-15% of patients will require non-cardiac surgery in the first year after stenting. Recent findings have suggested that prolonging DAPT beyond 12 months in patients with DES is not much more efficient than ASA monotherapy in reducing the incidence of a major adverse cardiac event (31). These patients will be at high risk of bleeding if DAPT is not stopped, at high risk of TE event if DAPT is stopped and there are consequences of delaying the surgery. Because of this complexity, a multidisciplinary approach and the team work of the cardiologist, anesthesiologist and surgeon is required (15). Whether or not AP therapy is discontinued, surgery is a proinflammatory and prothrombotic condition and the risk of thrombosis in the stent segment as well as in the rest of the coronary vasculature is increased. Therefore, it is best to postpone the surgery until the expiration of the DAPT, whenever possible. In other cases leave aspirin unless contraindicated (when risk of bleeding is very high, e.g. neurosurgery). In patients at moderate TE risk (an exception is surgery with a small risk of bleeding), stop P2Y12 inhibitors three to seven days before the intervention (ticagrelor–three to five days, clopidogrel–five days and prasugrel–seven days). They should resume the therapy as early as possible, preferably 24 hours after intervention. In patients with high risk of TE event strategy will depend on BL risk. If the BL risk is low, DAPT should not be stopped. Cases with moderate and high risk of bleeding are more complicated and require individual evaluation by a multidisciplinary team. Non-cardiac surgery should be postponed until DAPT is over, unless this poses a functional risk or is life-threatening to the patient. This postponement should last six months after myocardial infarction or after stent implantation with a high risk of thrombosis. If it is not possible, it is recom-mended to postpone non-cardiac surgery for at least one month, no matter the indication or the type of stent.

If it is not possible to postpone surgery for even a month, the intervention needs to be done in a hospital with catheterization room. If both AP drugs are excluded within the first month of stent placement, a bridging strategy with some of the intravenous AP drugs may be considered. NSAIDs should not be used in the perioperative period (Figure 2) (20, 32, 33).

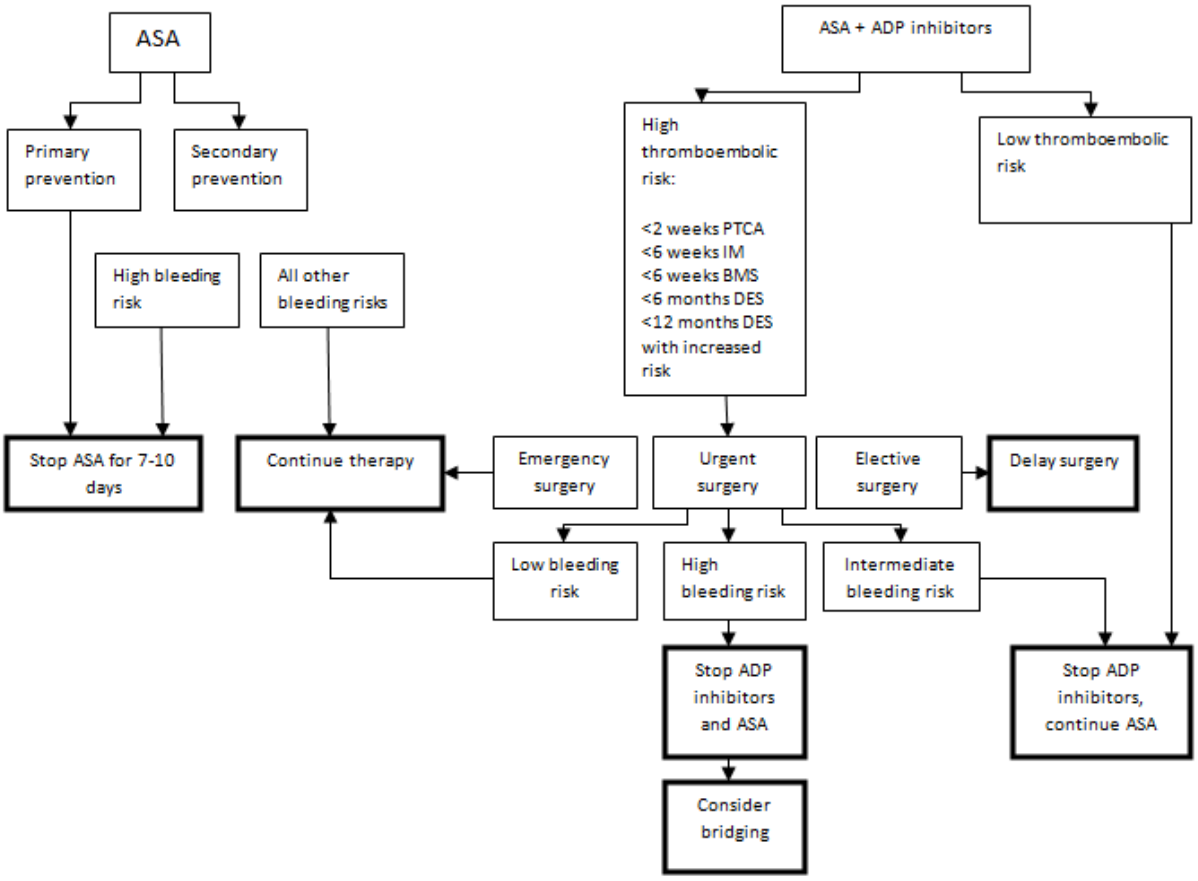

Figure 2. Algorithm for preoperative management of antiplatelet therapy

Timing of antiplatelet interruption

When ASA is prescribed for AF or primary prevention of myocardial infarction, therapy may be discontinued seven to ten days prior to surgery, while in those taking ASA for secondary prevention, discontinuation of therapy carries an increased risk of complications from the cardiovascular system. It has not been noted that perioperative ASA therapy causes increased bleeding or increased mortality, except in operations with a high BL risk. Therefore, the 2012 ACCP guidelines on perioperative management of antithrombotic therapy recommended not to discontinu ASA during the perioperative period in patients at high risk of cardiovascular events (5). Like ASA, when used for primary prevention of the cardiovascular or cerebrovascular event or for the AF, ADP inhibitors may be stopped preoperatively without major sequelae. ADP receptor inhibitors are most commonly administered before and after PCI with stent placement. In such patients, who undergo elective surgery, an adequate period of time after stent implantation is required for the surgery to be performed safely. Three to seven days before surgery is enough to reverse the effect of the ADP inhibitors (ticagrelor–three to five days, clopidogrel–five days and prasugrel–seven days) and they should be replaced with ASA whenever possible (14, 20).

Bridging in patients on antiplatelet therapy

There are few published studies and scarce clinical experience regarding bridging in patients who are taking AP drugs. Only when urgent surgery associated with a moderate or high BL risk is required and the patient has a high risk of thrombosis, the therapy can be continued. If the bridging is necessary, the recommendation is to use antithrombotics over AC drugs. Antithrombotic agents that have been studied so far are glycoprotein IIb/IIIa inhibitors (eptifibatide and tirofiban) and

P2Y12 inhibitor (cangrelor). Glycoprotein IIb/IIIa inhibitor should be started 72 hours after discontinuation of P2Y12 inhibitor. The recommended dose for tirofiban is 0.1 mcg/kg/min and 2 mcg/kg/min for eptifibatid. It should be discontinued four to six hours prior to surgery (34). P2Y12 inhibitor cangrelor should be started at least 48 hours after discontinuation of P2Y12 inhibitor and stopped 1-6 hours before surgery. The recommended dose is 0.75 μg/kg/min (34, 35).

Neuraxial anesthesia

One of the most serious complication of spinal and epidural anesthesia is spinal and epidural hematoma. Epidural anesthesia carries a higher risk, especially if a catheter is inserted. Because of increased BL risk, this type of anesthesia should not be used in patients on AT drugs. This risk is increased during catheter insertion as well as catheter removal. If neuraxial anesthesia is indicated, plan about stopping AT drugs must be made. The following recommendations are based on the 2022 guidelines for regional anesthesia in patients on antithrombotic drugs published by the European Society of Anesthesiology (36).

1) VKA: when INR is < 1.5.

2) DOACs: in low doses: last dose should be given minimum of 24 h for rivaroxaban and edoxaban, for apixaban 36 h and 48 h before puncture for dabigatran. If DOACs are administered in high doses, the last dose should be 72 h before puncture at least. In patients with impaired renal function (CrCl < 50 ml/min in high dose dabigatran therapy or CrCl < 30 ml/min in high dose direct anti Xa inhibitor therapy) preoperative laboratory test should be performed.

3) If LMWH is administered in low dose, then the last one should be at least 12 h before puncture. It is recommended that the low dose of LMWH should be halved or the last dose should be administered 24 h before the procedures in case CrCl < 30 ml/min. If LMWH is administered in high doses, the last dose should be given at least 24 h before puncturing. If LMWH is administered in high doses and CrCl < 30 ml/min the last dose should be administered 48 h before puncturing or dose should be halved.

4) For low doses of SC UH, the last dose should take place 4 h before puncture. When patient is receiving high doses of SC UH, aPTT have to be within normal range before puncture and last dose should take place 12 h before puncture. When patient is receiving high doses of IV UH last dose should take place 6 h before puncture.

5) Aspirin in doses < 200 mg is not contraindicated for performing neuraxial blockade.

6) P2Y12 inhibitors: in patients on ticagrelor the last dose should be given at least 5 days before the procedure, 5-7 days in patients on clopidogrel and 7 days in patients on prasugrel.

Conclusion

AT management plan should be made to reduce the risk of thrombosis on the one hand and bleeding on the other hand. For patients who have a VKA in their therapy that needs to be discontinued, a decision has to be made whether only withholding the AC drug would be enough or perioperative bridging with a short-acting agent is needed. Physicians' preference for routine perioperative bridging during chronic anticoagulation interruption has to be avoided. DOACs have shorter half-lives, but the laboratory tests for their activity and reversal agents is still hard to reach. In some of them, such as dabigatran, the drug effect is prolonged if renal insufficiency is present. Aspirin does not need to be stopped if the patient receives it for secondary prevention, exceptions are procedures with very high BL risk. It is best to postpone the surgery until the expiration of the DAPT, whenever possible. One of the most serious complication of spinal and epidural anesthesia is spinal and epidural hematoma. It is important to determine adequate timing of AT administration in relation to neuraxial anesthesia. The effects of AT agents should be withdrawn. Catheter manipulations and removal carry the same risk as insertion and the same criteria are used. Renal function must be considered for dabigatran and LMWH.

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PREOPERATIVNA PRIPREMA BOLESNIKA NA HRONIČNOJ ANTITROMBOTIČKOJ TERAPIJI ZA ELEKTIVNU NESRČANU HIRURGIJU

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Preoperativna priprema bolesnika na antitrombotičkoj terapiji (antiagregaciona i antikoagulantna terapija) izazovna je, zbog toga što prekid terapije nosi rizik od tromboembolijskog događaja, a operacija je povezana sa rizikom od krvarenja. Mora se napraviti balans između tromboembolijskog rizika i rizika od krvarenja i doneti odluka o tome da li će antitrombotička terapija biti prekinuta. Svaki bolesnik zahteva individualan pristup. Ovo znači izračunavanje tromboembolijskog rizika i rizika od krvarenja za svakog bolesnika. Rizik od krvarenja je zasnovan na individualnim karakteristikama bolesnika i riziku koji nosi sama hirurška intervencija. Tromboembolijski rizik je kompleksniji za izračunavanje. Ukoliko je doneta odluka da se prekine antitrombotička terapija, sledeće pitanje je koliko pre operacije treba biti prekinuta i da li neophodno premošćavanje.

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Ključne reči: *antitrombotička terapija, tromboembolijski rizik, rizik od krvarenja*