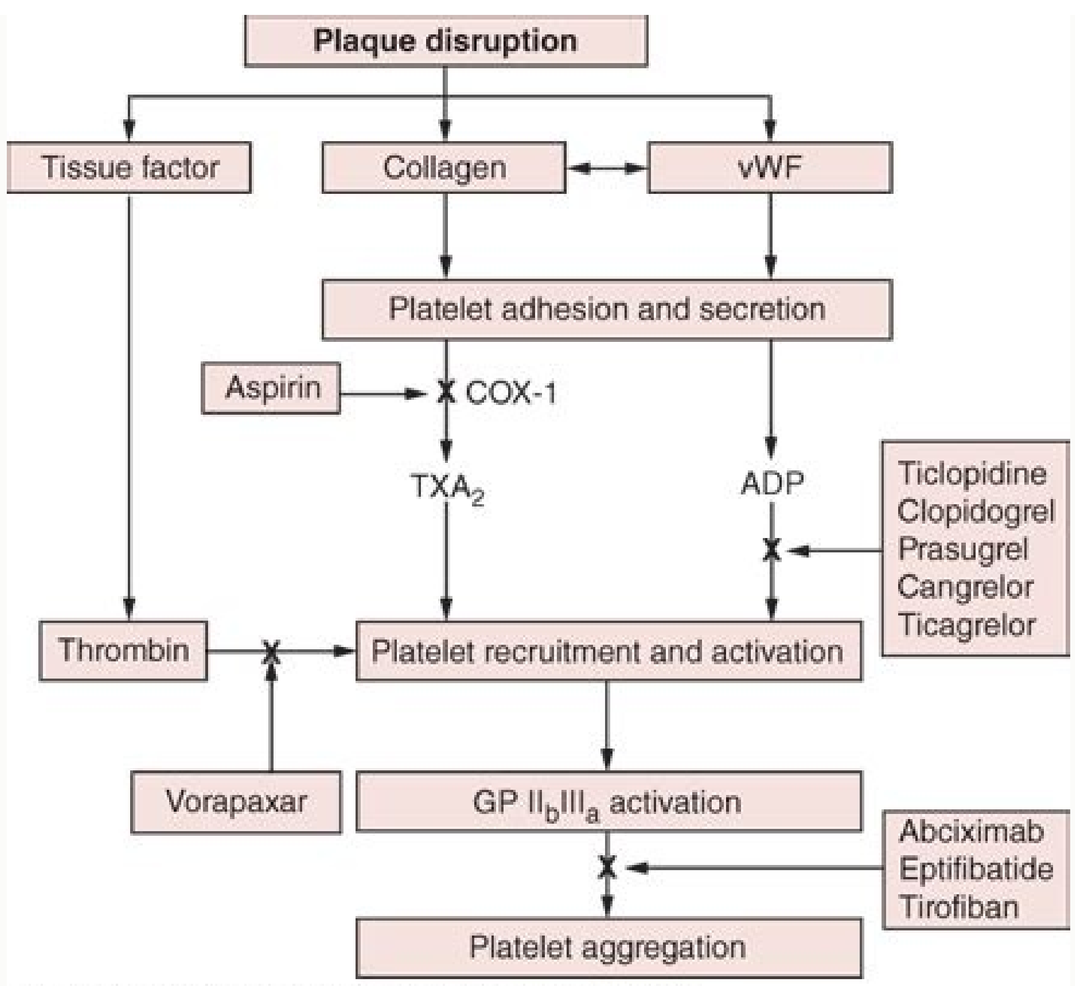
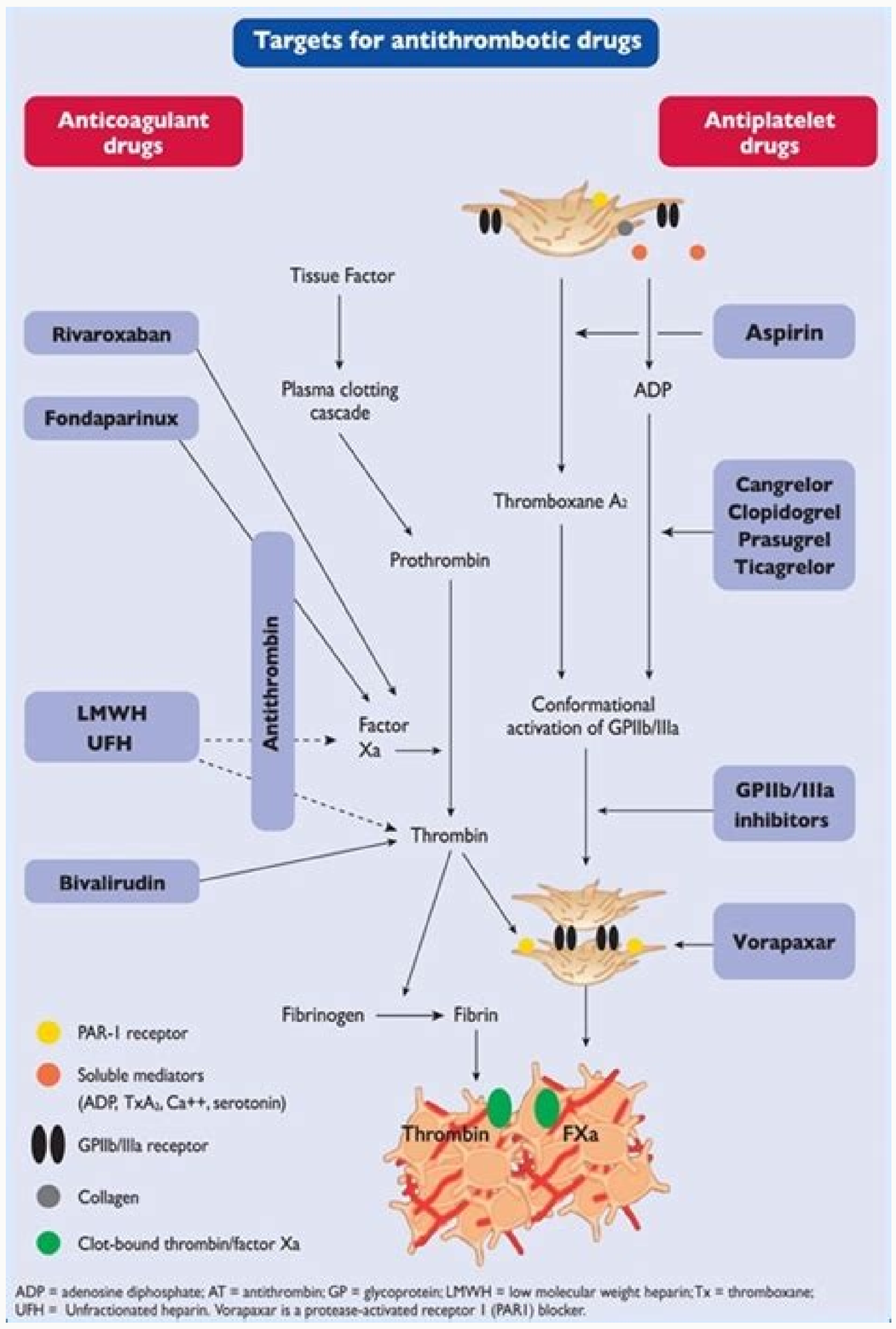
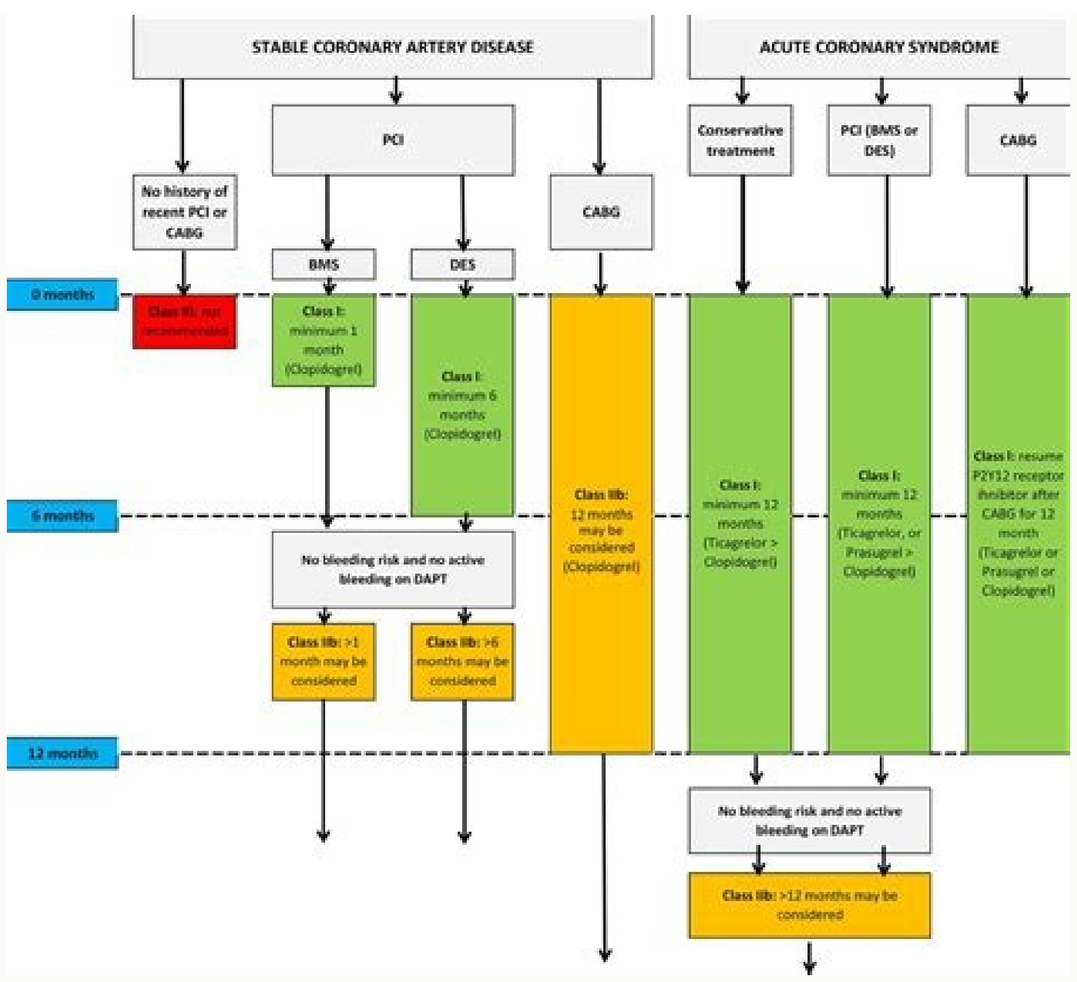
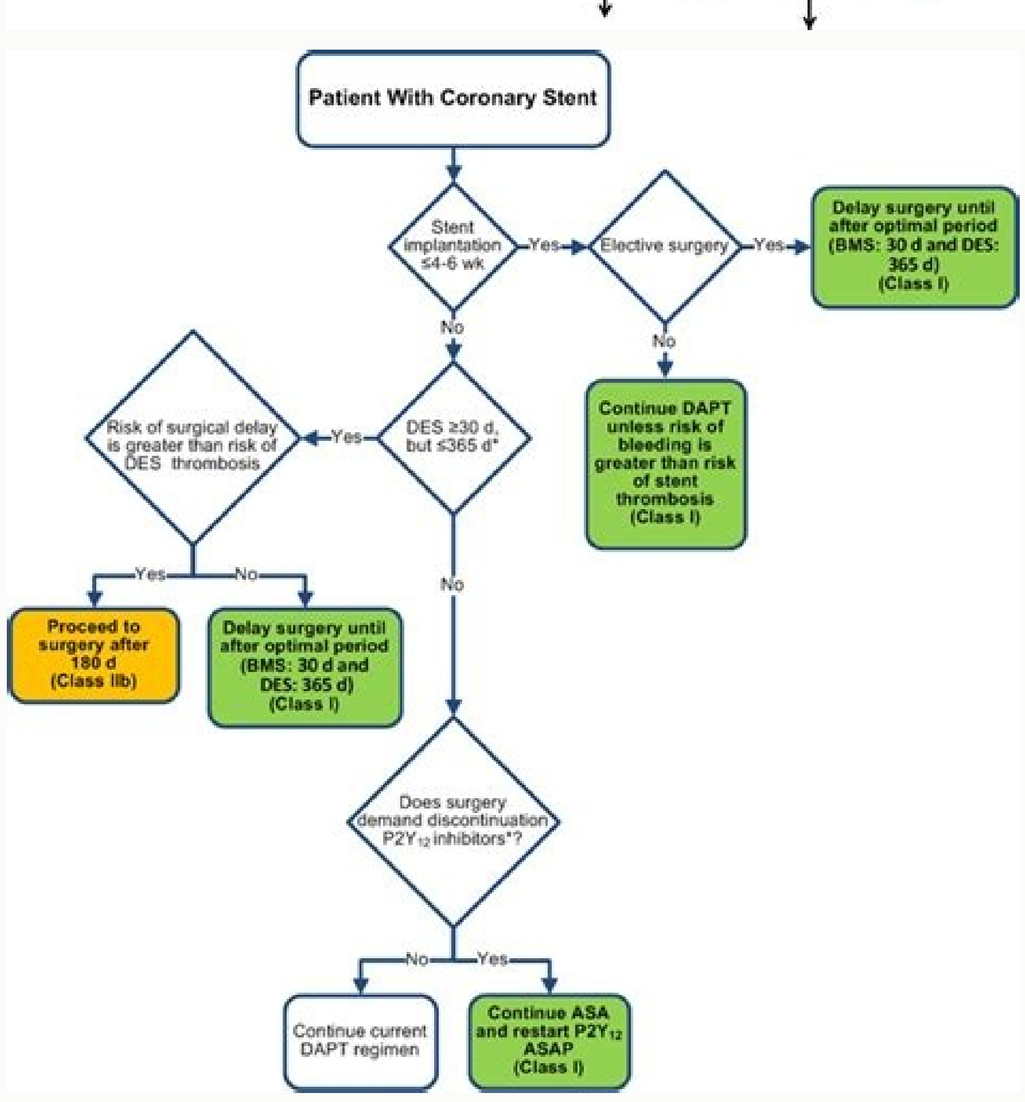
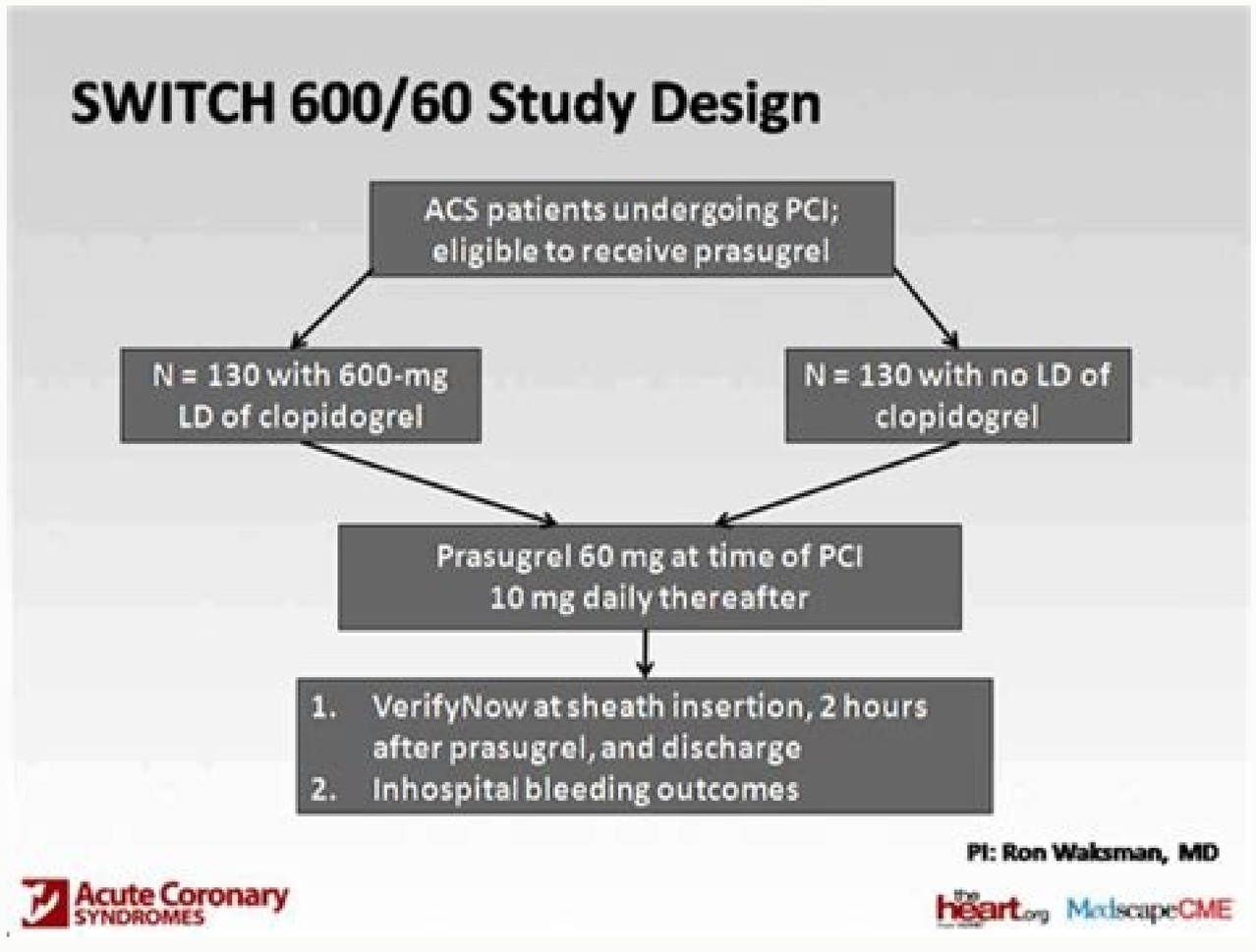
Perioperative antiplatelet therapy guidelines











Perioperative management of anticoagulation and antiplatelet therapy guidelines. Perioperative dapt guidelines. Dual antiplatelet therapy guidelines perioperative. Perioperative antiplatelet therapy guidelines ppt. Guidelines for antiplatelet therapy. Perioperative management of antiplatelet therapy guidelines.

 Worldwide, cardiovascular events represent the major cause of morbidity and mortality. A key role in the pathogenesis of these events is played by platelets. Interventional procedures, with placement of coronary and vascular stents, often represent the preferred therapeutic strategy. Antiplatelet medications are considered first-line therapy in preventing cardiovascular thrombotic events. A wide array of antiplatelet agents is available, each with different pharmacological properties. When patients on antiplatelet agents present for surgery, the perioperative team must design an optimal strategy to manage antiplatelet medications. Each patient is stratified according to risk of developing a cardiovascular thrombotic event and inherent risk of surgical bleeding. After risk stratification analysis, various therapeutic pathways include continuing or discontinuing all antiplatelet agents or maintaining one antiplatelet agent and discontinuing the other. This review focuses on the pharmacological and pharmacokinetic properties of both older and novel antiplatelet drugs, and reviews current literature and guidelines addressing options for perioperative antiplatelet management. Antiplatelet medications are commonly used by high-risk patients presenting for invasive procedures.Both continuation and discontinuation of antiplatelet therapy can be associated with significant risks.A team-based approach to risk stratification is critical to optimizing the perioperative approach to antiplatelet therapy.Antiplatelet agents, used as monotherapy or in combination, have a major role in preventing and managing cardiac and vascular events.1 These medications are of particular relevance, as coronary artery disease and stroke represent the top two causes of mortality worldwide, as reported by the World Health Organization in a report updated in 2013.2 Furthermore, the same report shows an increase in mortality as a result of such events in this decade when compared with the previous one. Physicians are encountering patients who are older and sicker than previously, and anaesthesiologists frequently encounter patients on medications affecting platelet function in the perioperative period. Understanding the indications, pharmacokinetics and pharmacodynamics of these agents allows physicians to anticipate and address possible undesired effects of continuing or discontinuing antiplatelet agents within this time frame.3 Role of the activated platelet in coagulation Atherothrombosis, a systemic disseminated process affecting the entire vascular tree, represents the underlying aetiology for both coronary and cerebral thrombotic events. However, the substrate for thrombus formation is atherosclerosis. Platelet activation represents the key step in the thrombotic process. The activated platelet plays not only an important role in the initiation and progression of atherosclerotic disease, but also has a quintessential role in the development of atherothrombosis, being implicated in endothelial, thrombotic, immune, and inflammatory responses.4 Recent evidence suggests that platelets also have a new and previously unsuspected role in tissue repair and vascular remodelling.5In their inactive state, platelets do not adhere to the endothelial wall or to each other. Endothelial activation leads to exposure of collagen to blood and von Willebrand factor. Platelet surface glycoprotein receptors [glycoprotein (GP) Ib–V–IXa, GP Ia/IIa and IV] interact with these components and promote platelet adherence to the vascular subendothelium and subsequent activation. The activated platelet undergoes conformational changes that result in degranulation of dense and alpha vesicles with the release of adenosine diphosphate (ADP), thromboxane A2 (TxA2), and thrombin. These platelet-activating substances lead to a conformational change in the GP IIb/IIIa receptor and its expression on the platelet membrane. Its surface expression leads to binding of other platelets through fibrinogen bridges. Subsequent to the release of platelet products (i.e. thrombin, platelet activating factor, ADP, TxA2), neighbouring platelet activation and recruitment occurs, rapidly forming a platelet aggregate. This interacts with fibrin and thrombin and promotes thrombus formation.6 Moreover, activation of ADP receptors severely blunts the antiaggregant and vasodilatory effects of nitric oxide and prostaglandin (PG) I2, to which inactive platelets are constantly exposed.7The role of the platelet in the coagulation cascade was defined more recently. Thrombin is generated through activation of factor VII by phosphate released from the dense granules. Moreover, the activated platelet provides the necessary surface for activation of other clotting factors and further promotes thrombus formation. In the inactive state, phosphatidylserine is present on the inner layer of the platelet membrane. Subsequent platelet stimulation results in its exposure on the outer layer, thus interacting with the factor Va–Xa complex and ultimately leading to thrombin formation.8Additionally, proinflammatory effects of platelets have received attention lately as critical steps in the initiation of atherosclerosis. Activated platelets release bioactive substances into the local microenvironment, which modify the adhesive and chemotactic properties of endothelial cells. Increased chemotaxis enables monocytes and other leucocytes to adhere and transmigrate through the endothelium to inflammatory sites.9Owing to both the key role of platelets in thrombus formation and their activation via multiple receptors (ADP, GP IIb/IIIa) and pathways (thromboxane formation), a variety of agents targeting different steps in this process have been developed. While aspirin (ASA) is a well-established antiplatelet agent targeting TXA2 formation, newer drugs protect against thrombosis by interfering with GP IIb/IIIa and ADP receptors10 (Fig. 1). In addition, newer agents targeting pathways responsible for thrombin formation (direct thrombin inhibitors or factor Xa inhibitors) are being investigated as potential adjuncts to antiplatelet drugs.11 Open in new tabDownload slideTherapies targeted at inhibiting various platelet receptors. These include the thromboxane inhibitors, ADP receptor antagonists, and GPIIb/IIIa inhibitors. Adapted from Meadows and Bhatt,4 with permission. TxA2, thromboxane A2; GP Ia/IIa, glycoprotein Ia/IIa; GP VI, glycoprotein VI; GP Ib-IX-V, glycoprotein Ib-IX-V; ADP, adenosine diphosphate; GP IIb/IIIa, glycoprotein IIb/IIIa.This review focuses on both old and novel antiplatelet drugs, including their pharmacology, indications, and possible perioperative management strategies. Specific drugs Aspirin Pharmacology ASA is an anti-inflammatory and antiplatelet agent whose effect is mediated through irreversible inhibition of cyclooxygenase 1 and 2 (COX1 and COX2). Its antithrombotic effect is primarily due to the inhibition of COX1, which is responsible for inhibiting PGH2 formation from arachidonic acid. PGH2 is the precursor for TxA2 formation by platelets (platelet aggregant and vascular vasoconstrictor), and PGI2 by endothelial cells (vascular vasodilator and antithrombotic).12 The doses required for its anti-inflammatory effects (mediated by COX2 inhibition) are much higher than the ones required for its antiplatelet effect (75–150 mg day−1). Doses as low as 20–40 mg of ASA a day can inhibit TxA2 formation in healthy volunteers for up to 1 week, with no antithrombotic benefit noted in patients receiving doses more than 1500 mg day−1.13ASA is rapidly absorbed through the enteric mucosa, with peak plasma level attained within 30–40 min for regular preparations and a half-life of 20 min14 (Table 1). While antiplatelet effects can usually be detected within an hour, enteric-coated preparations slow the rate of absorption that can lead to suboptimal antiplatelet effects in obese patients.15–19 The irreversible inhibition of COX1 maintains the antithrombotic effects of ASA for the lifespan of the platelet (7–10 days), with slow recovery of overall platelet function of 10% per day due to new platelet formation. Table 1Major characteristics of traditional and newer antiplatelet medications Drug . Mechanism of action . Loading dose . Maintenance dose . Half-life . Time to recover platelet function after drug withdrawal . Platelet inhibition . Administration route . Aspirin COX-1 inhibition 325 mg 75–325 mg daily 15–20 min 30% at 48 h Irreversible inhibition Oral Clopidogrel P2Y12 receptor inhibition 300–600 mg 75 mg daily 7–9 h 40% at 3 days Irreversible inhibition Oral Prasugrel P2Y12 receptor inhibition 60 mg 10 mg daily 7 h 2–3 days Irreversible inhibition Oral Ticagrelor P2Y12 and (partly) P2Y1 receptor inhibition 180 mg 90 mg twice a day 7–9 h 57% at 24 h Reversible inhibition Oral Cangrelor Adenosine triphosphate analogue with a high affinity for the P2Y12 receptor 30 μg kg−1 2–4 μg kg−1 min−1 3–6 min Rapid (minutes to hours) Reversible inhibition I.V. Abciximab Glycoprotein IIb/IIIa receptor inhibitor 0.25 mg kg−1 0.125 mg kg−1 min−1 10–15 min 12 h Reversible inhibition I.V. Eptifibatide Glycoprotein IIb/IIIa receptor inhibitor 180 μg kg−1 2 μg kg−1 min−1 2.5 h 2–4 h Reversible inhibition I.V. Tirofiban Glycoprotein IIb/IIIa receptor inhibitor 0.4 μg kg−1 0.1 μg kg−1 min−1 2 h 2–4 h Reversible inhibition I.V. Indications and efficacy Coronary artery disease Primary prevention In several trials, ASA therapy in doses of 75–325 mg daily demonstrated a 36–44% reduction in the rates of subsequent myocardial infarction (MI) with no increase in mortality. Newer data are not as convincing for the use of ASA in primary prevention.20–23 The United States Preventive Services Task Force recommends ASA 75 mg daily in patients 80% of pre-treatment value occurs at ~4 h after stopping drug infusion. Tirofiban has a plasma half-life of 1.5–2 h. It is removed by both renal and biliary excretion. Patients with renal insufficiency require dose adjustment of tirofiban86 (Table 1).The main difference between abciximab and the smaller molecules tirofiban and eptifibatide is the rate at which they dissociate from GP IIb/IIIa receptors (hours for abciximab vs seconds for tirofiban and eptifibatate). In addition, the lower affinity of eptifibatide for GP IIb/IIIa receptors compared with tirofiban means that a greater concentration of the former is required to achieve the same degree of IPA.87 Indications and efficacy The 2012 ACCF/AHA Focused Update of the Guideline for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction recommend the use of i.v. GP IIb/IIIa inhibitors in combination with ASA and heparin, both in patients treated medically and interventionally.27,88 The 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction recommends, as a reasonable approach,

initiation of therapy with heparin and an i.v. GP IIb/IIIa receptor antagonist such as abciximab (Level of Evidence: A), high-bolus-dose tirofiban (Level of Evidence: B), or double-bolus eptifibatide (Level of Evidence: B) at the time of PCI.28Many studies have evaluated the efficacy of i.v. GP IIb/IIIa inhibitors in ACS. A meta-analysis involving 21 trials concluded that GP IIb/IIIa inhibitors significantly reduce the combined endpoint of death, non-fatal MI, or urgent revascularization at 30 days in patients undergoing PCI. Similar outcomes were identified in patients with medically treated NSTEMI and in patients with STEMI treated with angioplasty.89 Risks The rates of bleeding encountered with GP IIb/IIIa inhibitor therapy have been higher than those seen with placebo.90 A pooled analysis of 14 randomized studies including a total of 28 000 patients treated with heparin and a GP IIb/IIIa inhibitor or placebo found that the incidence of intracerebral haemorrhage was similar between the two groups. Moreover, no difference was identified when treatment with a GP IIb/IIIa inhibitor alone was compared with heparin alone.91 Perioperative management of antiplatelet agents Perioperative management of antiplatelet agents is complex, so the team of perioperative clinicians (anaesthesiologist, surgeon, and prescribing physician—either neurologist or cardiologist) should participate in decision-making. Several factors need to be considered before a decision to continue or stop antiplatelet agents perioperatively. An important factor is the initial indication for antiplatelet therapy and, most importantly, the consequences of stopping the drug before the operation. Premature discontinuation of antiplatelet agents including GP IIb/IIIa inhibitors is associated with an increase in thrombotic events due to a rebound effect on platelet activation.92,93 The other important factor to consider is the inherent bleeding risk of certain procedures and the impact of bleeding on overall patient outcome (Table 2). Table 2Bleeding risk in non-cardiac surgery Surgical haemorrhagic risk . Blood transfusion requirement . Type of surgery . Low Usually not required Peripheral, plastic, and general surgery biopsies Minor orthopaedic, otolaryngology, and general surgery Endoscopy Eye anterior chamber Dental extraction and surgery Intermediate Frequently required Visceral surgery Cardiovascular surgery Major orthopaedic surgery Otolaryngology Urological surgery Reconstructive surgery High Possible bleeding in a closed space Intracranial neurosurgery Spinal canal surgery Eye posterior chamber surgery Based on the role of platelets in the coagulation cascade, various point-of-care testing devices have been developed. However, there are differences in the sensitivity of these tests in assessing recovery of platelet function after discontinuation of ADP receptor inhibitors and significant interindividual variability in results. Therefore, the role of these tests in strategies for perioperative management of antiplatelet agents is evolving.94 Aspirin In patients on ASA for AF or for primary prevention of MI and stroke, the drug can be stopped 7–10 days before operation without major consequences. In patients on ASA for secondary prevention, discontinuation is associated with increased risk of cardiovascular complications [odds ratio (OR) = 3.1], peaking at 8–10 days for coronary thrombosis and 14 days for cerebrovascular events.95 For patients who have undergone PCI with stenting, the likelihood of ST is much higher (OR= 90) when ASA is discontinued.95–97Bleeding risk has been assessed in a meta-analysis involving 49 590 patients on low-dose ASA, with results ranging from very little bleeding for dermatological, ophthalmological, visceral, minor abdominal, endoscopic, dialysis catheter insertions, and minor dental procedures to 75% in patients undergoing transurethral prostate biopsy. A large trial on patients undergoing orthopaedic surgery (hip replacement) reported an increase in GI bleeding and a decrease in postoperative haemoglobin (average of 2 g litre−1), and also an increased need for blood transfusions (53 ml on average). Despite that, there was no increase in mortality.98Orthopaedic patients undergoing spinal fusion or femoral neck fractures had no increase in bleeding.99–101 Patients undergoing tonsillectomy have a 7.2-fold increase in rates of reoperation for haematomata compared with those not on ASA.102Vascular surgery patients have a small increase in bleeding complications.103 Newer studies, in high-risk patients on low-dose ASA undergoing non-cardiac surgery, show a decrease in MACE, but no overall increase in bleeding complications.40,104,105In patients undergoing cardiac surgery, preoperative ASA administration increases postoperative bleeding and red blood cell requirements with no effect on mortality, re-exploration rate, and perioperative MI.106 A new meta-analysis concluded that ASA was associated with increased chest tube drainage in this patient population and might be associated with a greater requirement for blood products.41 Patients on ASA have a 2.7-fold increase in blood transfusion rates during transurethral prostatectomy compared with placebo.107 In neurosurgical procedures, ASA use has led to increased mortality.102,108In conclusion, with the exception of high-risk bleeding procedures (intracranial and medullary canal surgery, posterior chamberof the eye surgery, and transurethral prostate resection), ASA continuation perioperatively is not associated with significant bleeding events or with increased mortality.47,99,109 Therefore, the 2012 ACCP guidelines on Perioperative Management of Antithrombotic Therapy recommend continuing ASA in the perioperative period for patients at high cardiovascular risk55 (Fig. 2). Open in new tabDownload slideAlgorithm for perioperative management of antiplatelet therapy. Adapted from Di Minno and colleagues,99 with permission. ADP, adenosine diphosphate; ASA, aspirin; PTCA, percutaneous transluminal coronary angioplasty; BMS, bare metal stent; DES, drug-eluting stent; MI, myocardial infarction; ST, stent thrombosis. ADP receptor inhibitors As with ASA, when the ADP receptor inhibitors are recommended for treatment of AF or primary prevention of cardiac or cerebrovascular events, these agents can be stopped before operation without major consequences.47 On the other hand, ADP receptor inhibitors are a major component of the DAPT recommended pre- and post-PCI with stenting. Several aspects need to be considered in patients with stents undergoing surgery: the appropriate time frame after stent placement before surgery can be safely performed, the potential consequences of stopping DAPT, the urgency of the intervention, and the bleeding risk associated with the intervention.110 Recommended duration of DAPT after PCI Many studies have revealed that premature discontinuation of DAPT before the recommended interval necessary for complete endothelialization of the stent can lead to fatal consequences.111 Studies in DES patients demonstrated that premature discontinuation of clopidogrel was the most important factor leading to early ST (hazard ratio of 57) and fatal outcomes (mortality 45% for patients developing ST).112 Late ST has also been linked to discontinuation of clopidogrel after 1 yr of DAPT.113The perioperative period is marked by a prothrombotic state due to increased levels of circulating fibrinogen and C-reactive protein.114,115 This hypercoagulable state leads to increased atheromatous plaque instability, which, in association with premature discontinuation of the ADP receptor inhibitor, can have dire consequences (mortality varying from 30% to 86%).116,117 These effects are augmented by an ADP receptor inhibitor discontinuation rebound phenomenon, clearly demonstrated for clopidogrel and also well described with ASA cessation, which is responsible for a cluster of thrombotic events.118The recommended duration for continuing DAPT in patients receiving PCI varies with different guidelines. While there is no controversy regarding the minimum duration of DAPT after balloon angioplasty only (2 weeks) and after BMS placement (4–6 weeks), the optimal duration after DES placement is uncertian.30,119 The 2007 ACC/AHA Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac surgery recommend a minimum of 12 months of uninterrupted DAPT after DES placement, whereas the 2010 ESC guidelines on myocardial revascularization and the 2012 ACCP guidelines on perioperative management of antithrombotic therapy endorse a minimum of 6 months.55,56,119 Initial data showed that discontinuation of clopidogrel 6 months after placement of a DES is associated with a 2–3 times higher incidence of late ST compared with patients receiving BMS.120,121 However, more recent literature suggests that prolonging DAPT for a period longer than 12 months in DES patients is not significantly more effective than ASA monotherapy in reducing the rate of MACE.122The question of 6 or 12 months of DAPT after DES placement was recently addressed in several trials. A prospective trial involving 1443 DES patients receiving either 6 or 12 months of DAPT showed that the risk of target vessel failure at 12 months is similar.123 Another randomized trial including 2013 patients with BMS and DES demonstrated that a regimen of 24 months compared with 6 months of clopidogrel therapy was not more effective in reducing the composite endpoint of death due to any cause, MI, or stroke.124 Newer data evaluate the safety of discontinuing DAPT after 3 months after placement of a zotarolimus-eluting stent (second-generation DES). In a randomized study of 2117 patients, 3 months of DAPT were non-inferior compared with the standard 12 months therapy in the occurrence of the primary endpoint at 1 yr (cardiovascular death, MI, ST, target vessel revascularization, or bleeding).125 This was confirmed in a smaller study of 128 patients.126While the above data were obtained outside the peri-procedural area, similar outcomes have also been recorded perioperatively.127 A population cohort study of 8000 patients undergoing major elective procedures who had BMS or DES placed up to 10 yr prior concluded that the fewest complications occurred when the patient underwent surgery between 6 months and 1 yr after DES placement.128As a result, it is still unclear what is the optimal duration of DAPT and timing of surgery. The key to these questions is the individual risk for delayed stent endothelialization. Several clinical predictors for delayed endothelialization and thrombosis of DES have been identified: presence of ACS, treatment of bifurcating lesions, presence of multiple and overlapping stents, left ventricular ejection fraction

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