CME

Antiplatelet Drugs: A Review of Their Pharmacology and Management in the Perioperative Period

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In the normal course of the delivery of care, anesthesiologists encounter many patients who are receiving drugs that affect platelet function as a fundamental part of primary and secondary management of atherosclerotic thrombotic disease. There are several antiplatelet drugs available for use in clinical practice and several under investigation. Aspirin and clopidogrel (alone and in combination) have been the most studied and have the most favorable risk-benefit profiles of drugs currently available. Prasugrel was recently approved for patients with acute coronary syndrome undergoing percutaneous interventions. Other drugs such as dipyridamole and cilostazol have not been as extensively investigated. There are several newer investigational drugs such as cangrelor and ticagrelor, but whether they confer significant additional benefits remains to be established. Management of patients who are receiving antiplatelet drugs during the perioperative period requires an understanding of the underlying pathology and rationale for their administration, pharmacology and pharmacokinetics, and drug interactions. Furthermore, the risk and benefit assessment of discontinuing or continuing these drugs should be made bearing in mind the proposed surgery and its inherent risk for bleeding complications as well as decisions relating to appropriate use of general or some form of regional anesthesia. In general, the safest approach to prevent thrombosis seems to be continuation of these drugs throughout the perioperative period except where concerns about perioperative bleeding outweigh those associated with the development of thrombotic occlusion. Knowledge of the pharmacodynamics and pharmacokinetics of antiplatelet drugs may allow practitioners to anticipate difficulties associated with drug withdrawal and administration in the perioperative period including the potential for drug interactions. (Anesth Analg 2011;112:292–318)

Anesthesiologists frequently encounter patients with atherothrombotic disease who are receiving drugs deliberately designed to impair the normal function of the coagulation system. The platelet is integral to the initiation of thrombosis.[1] Drugs that affect platelet function are a fundamental part of primary and secondary management of atherosclerotic thrombotic disease.[2] As reviewed in various guideline documents,[3] authoritative reviews, and meta-analyses, the indications for the use of antiplatelet drugs in the management of thrombotic diseases include stroke,[4–6] acute myocardial infarction (AMI),[7–9] acute coronary syndrome (ACS),[10,11] angina,[12] percutaneous coronary intervention (PCI),[13–15] cardiac surgery,[16–20] primary[21–23] and secondary cardiovascular disease prevention,[7,14,23–26] peripheral vascular disease,[27–31] and thrombotic disorders such as atrial fibrillation.[7,32] There are several antiplatelet drugs available for use in clinical practice and several under investigation (Fig. 1).[33] Management of patients who are receiving antiplatelet drugs during the perioperative period requires an understanding of the underlying pathology and rationale for their administration, pharmacology and pharmacokinetics, and drug interactions. The risk versus benefit assessment of continuing or discontinuing these drugs should be made bearing in mind the proposed surgery and its inherent risk for bleeding or thrombotic complications as well as decisions relating to appropriate use of general or some form of regional anesthesia. Reports of late coronary and carotid artery stent occlusion, particularly in the perioperative period after discontinuation of an antiplatelet drug,[34] have served to heighten concern about the perioperative management of these drugs. This review focuses on the perioperative use of some of the current and investigational drugs affecting platelet function (Table 1) by describing their pharmacology including pharmacokinetics, pharmacodynamics, and drug interactions of particular relevance, management in the perioperative period in light of the above reports, and areas where further research should occur. Where possible, suggestions are made about the perioperative management of these drugs for patients receiving general or regional anesthesia.

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Accepted for publication October 1, 2010.

Conflict of Interest: See Disclosures at the end of the article.

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DOI: 10.1213/ANE.0b013e318203f38d

ANTIPLATELET DRUGS

Aspirin

Aspirin has a central role in the prevention of thromboembolic complications from atherosclerotic disease and is the leading therapeutic drug for this purpose.[3,35]

Pharmacokinetics

After oral administration, aspirin is rapidly absorbed from the upper gastrointestinal (GI) tract with peak levels occurring

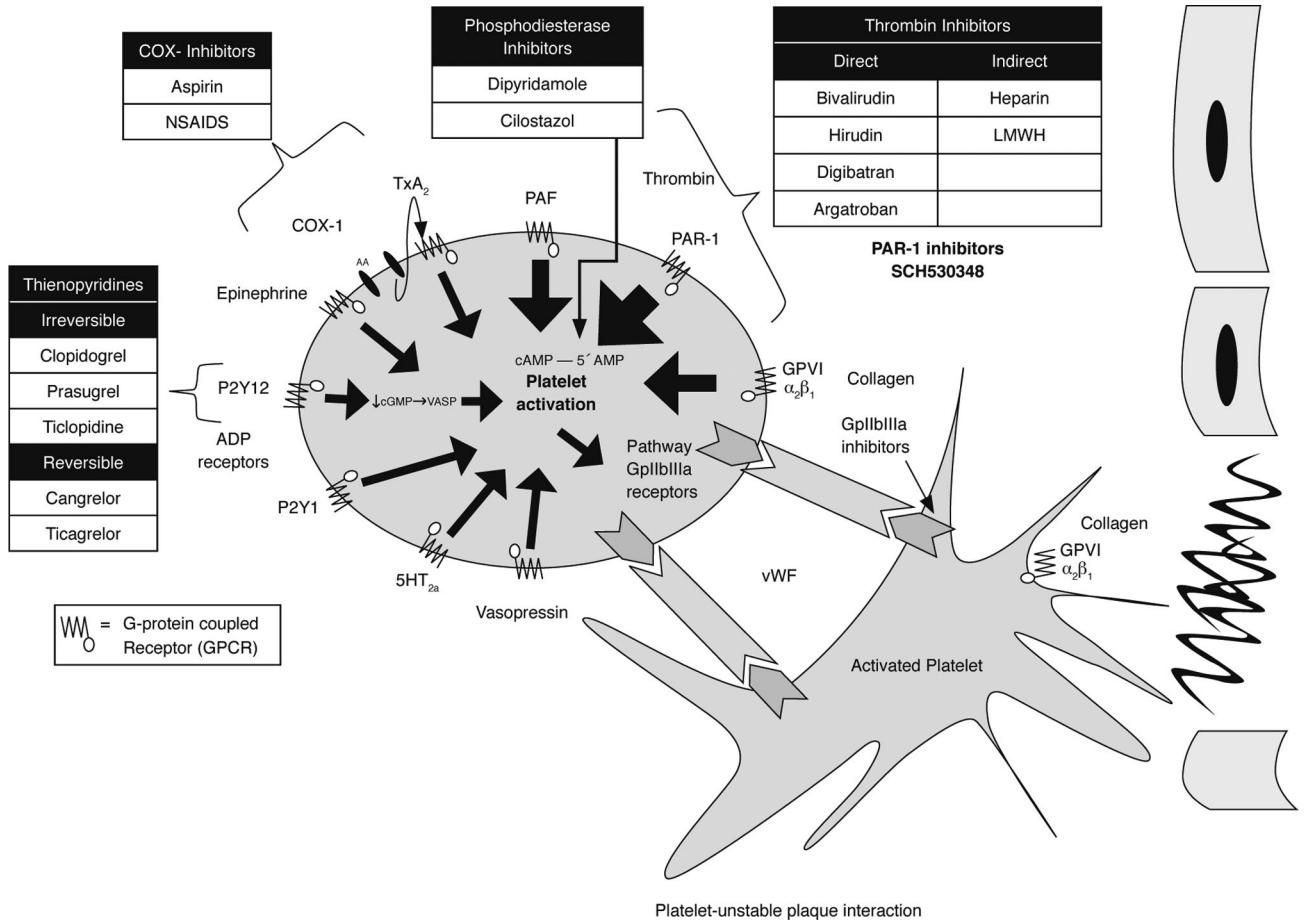

Figure 1. Agonists to platelet activation and antiplatelet drugs. COX = cyclooxygenase; NSAIDs = nonsteroidal antiinflammatory drugs; LMWH = low-molecular-weight heparin; TxA_2 = thromboxane A_2; PAR-1 = protease-activated receptor 1; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; ADP = adenosine diphosphate; VASP = vasodilator stimulated phosphoprotein; 5HT = 5 hydroxytryptamine; vWF = von Willebrand factor; 5′AMP = 5′ adenosine monophosphate; PAF = platelet aggregating factor; GP = glycoprotein; P = purinergic. (From Gladding et al.,[33] with permission.)

approximately 30 to 40 minutes after ingestion.[36] For the majority of patients, there does not seem to be any additional effect on platelet activity at doses >300 mg.[37] Use of enteric-coated formulations may considerably delay the time to peak effect.[38]

Pharmacodynamics

The effect of aspirin on platelet function is to permanently inactivate a key platelet enzyme (cyclooxygenase [COX]).[39] This effect can only be reversed by generation of new platelets[40] thus permitting once-daily dosing. Conditions for which aspirin is indicated and its lowest effective dose are given in Table 2.[35]

COX exists in 2 isoforms (COX-1 and COX-2[41]) and catalyzes the first step in prostanoid synthesis, the conversion of arachidonic acid to prostaglandin (PG)H_2. PGH_2 is rapidly converted to several bioactive prostanoids including thromboxane A_2 (TXA_2) and PGI_2.[41] Aspirin inhibits COX by diffusing into the COX channel within the membrane to the catalytic site for the enzyme (an arginine 120 residue, which is a common binding site for all COX inhibitors) and then acetylating a serine residue (serine 529 in human COX-1 and serine 516 in human COX-2). This prevents arachidonic acid from gaining access to the catalytic site of the enzyme.[42]

In response to various stimuli, platelets generate TXA_2, a process that is very sensitive to inhibition by aspirin[43] and largely mediated by COX-1. In contrast, the endothelium generates PGI_2, a process that is much less sensitive to inhibition by aspirin and largely mediated by COX-2.[35] As a consequence, low-dose aspirin has limited measurable effects on PGI_2-dependent vascular functions including arterial blood pressure regulation,[44] renal function,[45] or interference with the antihypertensive effects of diuretics and angiotensin-converting enzyme (ACE) inhibitors.[46] A daily dose of 30 mg aspirin is sufficient to completely suppress TXA_2 production within 1 week.[43]

Adverse Effects

The major adverse effect of aspirin administration is an increased risk of bleeding complications,[35,47] albeit with a very favorable risk-benefit ratio.[47] One of the most common sites for bleeding is the GI tract,[48] although this risk may be ameliorated by the use of gastroprotective drugs such as proton pump inhibitors (PPIs).[49]

Drug Interactions

The concomitant administration of nonselective reversible COX-1 inhibitors such as ibuprofen and naproxen may lead

Table 1. Properties of Current Oral and Investigational Antiplatelet Drugs

Drug	Class	Mechanism of action	Route of administration	Metabolism to active metabolite required	Route of elimination	Permanent platelet inactivation	Time required to recover adequate platelet function after drug administration
Aspirin	Salicylate	Cyclooxygenase enzyme inhibition	Oral	No	Liver, by deacetylation to salicylic acid	Yes	30% at 48 h
Clopidogrel	Thienopyridine	$P2Y_{12}$ receptor blockade	Oral	Yes	Liver, by a 2-step process involving CYP3A5/2CD19 to active metabolite	Yes	40% at 3 d
Ticlopidine	Thienopyridine	$P2Y_{12}$ receptor blockade	Oral	Yes	Liver, by CYP2CD19 to active metabolite	Yes	4–8 d
Prasugrel	Thienopyridine	$P2Y_{12}$ receptor blockade	Oral	Yes	Liver, by CYP3A4 to active metabolite	Yes	2–3 d
Elinogrel	Sulfonylurea	$P2Y_{12}$ receptor blockade	Oral, IV	No	Liver and kidney with minimal metabolism	No	8 h after a single 10-mg dose; longer with higher doses
Cangrelor	ADP analog	$P2Y_{12}$ receptor blockade	IV	No	Dephosphorylation	No	Rapid (min–h)
Ticagrelor	Cyclopentyltriazolopyrimidine	$P2Y_{12}$ receptor blockade	Oral	No	Liver, active metabolite	No	57% at 24 h
Dipyridamole	Phosphodiesterase inhibitor	PDE inhibition	Oral	No	Liver, enterohepatic recirculation	No	2 d (?)
Cilostazol	Phosphodiesterase III inhibitor	PDE III inhibition	Oral	No	Liver, CYP3A4/2CD19 active metabolite	No	2 d (?)
Terutroban	PAR-1 receptor blocking drug	PAR-1 blockade	Oral	No	?	?	?
E5555	PAR-1 receptor blocking drug	PAR-1 blockade	Oral	No	?	No	?
SCH-530348	PAR-1 receptor blocking drug	PAR-1 blockade	Oral	No	Liver, biliary excretion	No	?

ADP = adenosine diphosphate; PDE = phosphodiesterase; PAR-1 = protease-activated receptor 1.

Table 2. Disorders for Which Aspirin Has Been Shown to Be Effective and the Lowest Effective Daily Dose

Disorder	Lowest effective daily dose (mg)
Hypertension	75
Chronic stable angina	75
Polycythemia vera	100
Unstable angina	75
Acute myocardial infarction	160
Transient ischemic attack and ischemic stroke	50
Severe carotid artery stenosis	75
Acute ischemic stroke	160
Atrial fibrillation	325
Men at high cardiovascular risk	75
Immediate postcardiac surgery graft preservation	?325

Adapted from Patrono et al.,[35] with permission.

to impairment in the efficacy of aspirin.[42,50–53] There is competition between the nonselective COX inhibitors and aspirin for the common docking site within the COX-1 channel (arginine 120), which may prevent aspirin from acetylating the serine residue at position 529.[42] Such an interaction could occur in the perioperative period when these drugs are often coadministered. Retrospective cohort studies have not demonstrated any increased risk of myocardial infarction (MI) when ketorolac was administered postoperatively with antiplatelet drugs.[54] The coadministration of aspirin and COX-1 inhibitors after cardiac surgery has not been well studied. Given the potential for COX inhibitors (particularly COX-2 inhibitors[55]) to exacerbate ischemic heart disease[56–58] (including after cardiac surgery[59]), it is suggested that, until further research is done, where possible, analgesic drugs with minimal effects on COX (e.g., acetaminophen[42,56]) be considered particularly in patients who have undergone a PCI procedure with stent placement.

Aspirin "Resistance" and "High on Treatment Platelet Reactivity (HPR)"

No antithrombotic drug currently available is 100% effective in the prevention of adverse thrombotic events.[60] The incidence of true aspirin "resistance," defined as the inability of aspirin to inhibit COX-1–dependent TXA_2 production, is very low (approximately 1%–2%).[61] Current estimates suggest that up to 30% of treated individuals may, however, have an inadequate response to aspirin treatment at doses <300 mg daily,[62] and are susceptible to treatment failure. Treatment failure may be associated with significant adverse outcomes including death, MI, cerebrovascular accident, closure of saphenous vein grafts, and occlusion of peripheral arterial grafts.[63] The reasons for inadequate drug effect while on treatment have been investigated. Patient noncompliance with the prescribed medication may be a significant cause (3%–40%).[64] Indeed, studies reporting the incidence of treatment failure that have not controlled for noncompliance should be considered flawed methodologically.

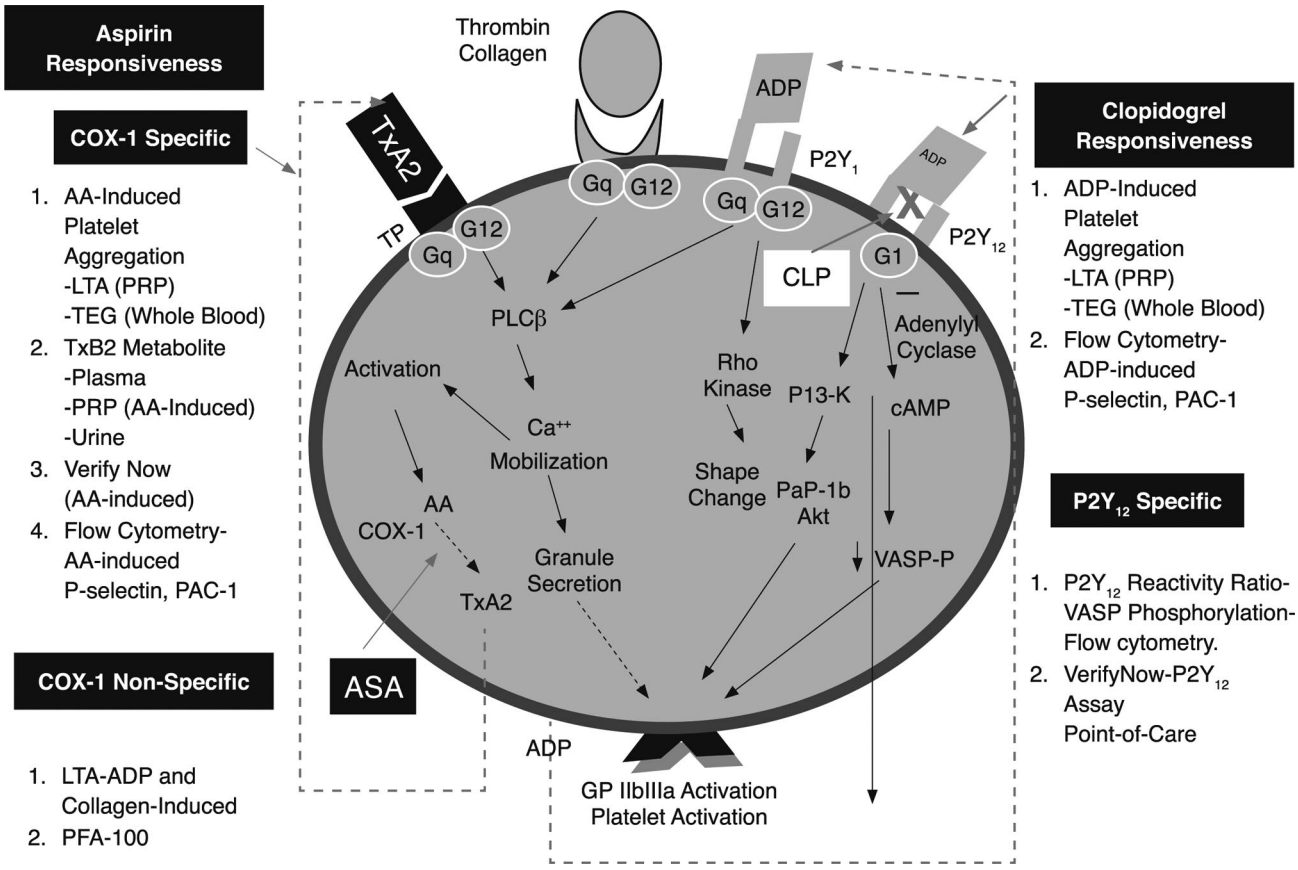

Figure 2. Mechanism of action and laboratory evaluation of clopidogrel and aspirin responsiveness. AA = arachidonic acid; ADP = adenosine diphosphate; COX-1 = cyclooxygenase-1; CLP = clopidogrel; LTA = light transmittance aggregometry; PRP = platelet-rich plasma; PAC-1 = activated glycoprotein IIb/IIIa receptor; PFA-100 = platelet function analyzer-100; PLC_{β} = $phospholipase_{\beta}$; ASA = aspirin; TP = thromboxane receptor; TxB2 = thromboxane B2; TEG® = thrombelastography; VASP-P = vasodilator stimulated phosphoprotein–phosphorylated. (From Gurbel and Tantry,[317] with permission.)

Moreover, failure to take antiplatelet drugs as prescribed may place patients at increased risk for thrombotic complications because of rebound platelet activation.[65] However, a number of patients have been observed to have inadequate response to aspirin treatment despite receiving doses considered adequate for the majority of patients. These patients are discovered by using an in vitro test of platelet function (Fig. 2) (with assay limits defined for the test by the investigator) and are described as having "high platelet reactivity (HPR)" or "biochemical resistance."[66] HPR is an ex vivo diagnosis based on testing and should be considered as a primary event. Clinical thrombosis is a very late sign of HPR if it is present, but is not definitive proof that HPR is the cause of thrombosis. Differences in thrombotic outcomes for patients whose antiplatelet dosing was based on ex vivo platelet function test results have been demonstrated.[63,67,68] HPR is measured differently using different tests and different values based on the drug being evaluated and the investigator definition.

Conditions associated with an inflammatory response such as unstable angina,[69] AMI,[70] diabetes,[71] and cardiac surgery[72] are associated with HPR in aspirin-treated patients. In animals, the development of atherosclerosis is accompanied by an inflammatory response mediated through the thromboxane pathway with generation of free radicals.[73] A link between direct measures of inflammation and increased thrombogenicity has recently been demonstrated.[74] Generation of inflammatory cytokines as part of the inflammatory response leads to endothelial and monocyte cell activation with expression of tissue factor, a potent stimulus for platelet activation.[75,76] In turn, activated platelets contribute to further inflammation by releasing other inflammatory mediators such as platelet activating factor.[77] Surgery leads to increases in catecholamines.[72,78] Catecholamines have been demonstrated to enhance the inflammatory response in vitro[79] and in an animal model,[80] and to increase platelet reactivity,[81,82] which is only partially responsive to inhibition by aspirin.[83]

Other possible mechanisms for HPR include genetic polymorphisms of the platelet glycoprotein receptor[84] and COX-1 and COX-2 alleles,[85] generation of aspirin-insensitive COX,[69] and increased platelet turnover.[86] In combination, these factors may lead to reduced aspirin effect[20,86] and increased risk for perioperative ischemic events.[87] In the perioperative period, although the effectiveness of aspirin to prevent thrombotic complications has been demonstrated,[16] its efficacy may be reduced in a substantial proportion of patients.[88]

Table 3. Possible Causes of Nonresponse to Aspirin or Clopidogrel

Specific for aspirin	Common to both aspirin and clopidogrel	Specific for clopidogrel
	Nonatherothrombotic causes of vascular event (e.g., arteritis, cardiac embolism)	
	Baseline individual variability • ↑ Baseline platelet reactivity • ↑ BMI • Diabetes/insulin resistance	
Reduced bioavailability Drug interaction: NSAIDs	**Reduced bioavailability** • Failure to prescribe • Poor compliance/inadequate intake • Underdosing • Variable absorption/metabolism	**Reduced bioavailability** Drug interaction: drugs metabolized by the cytochrome P-450 CYP3A4 system
	Increased platelet turnover • ↑ Platelet production (perioperative stress) • Exogenous administration (transfusion) • ↑ Platelet reactivity	
Genetic polymorphisms Platelet GP Ia/IIa Ib/V/IX, and IIb/IIIa receptors • Collagen, vWF • COX-1, -2 • Thromboxane A_2 • Factor XIII Val34Leu (↓ factor XIII activation)		**Genetic polymorphisms** • $P2Y_{12}$ H2 haplotype • CYP3A4 • CYP2C19
Alternate pathways of platelet activation • Activation by other pathways (e.g., catecholamines) • ↑ COX from nucleated cells • non-COX-thromboxane A_2 synthesis		
Tachyphylaxis		

NSAIDs = nonsteroidal antiinflammatory drugs; COX = cyclooxygenase; vWF = von Willebrand factor; BMI = body mass index; GP = glycoprotein.
Adapted from Michos et al.,[318] with permission.

Statistically, approximately 3% of patients should be expected to be hypo-responders based on their response to arachidonic acid testing.[89] The optimal management of patients with a true lack of response to aspirin has not been clarified.[90] It is mandatory to ensure that reversible causes of failure such as lack of compliance have been addressed.[35,91] Higher doses of aspirin may increase the number of aspirin responders as determined by response to in vitro tests of platelet function.[92] This has been observed clinically after cardiac surgery,[93] and increased aspirin doses have been associated with a reduction in graft failure in the postoperative phase after cardiac surgery.[94] The use of alternative antiplatelet drugs such as clopidogrel alone or in combination with aspirin might be considered.[95] However, the additional benefit obtained has been modest when examined in randomized clinical trials.[14] In addition, some patients with an inadequate response to aspirin may also have an inadequate response to clopidogrel (i.e., dual "resistance"), which may be particularly prevalent among women and diabetics.[96]

The term "aspirin resistance" has also been used to describe the inability of aspirin to protect individual patients from thrombotic complications (often referred to as clinical resistance).[35,97–99] Without biochemical confirmation, the occurrence of a thrombotic event in a patient while receiving aspirin therapy should more appropriately be labeled as a "treatment failure," which may have many causes other than the inability of aspirin to inhibit TXA_2 production (Table 3).[100] Given the multiple pathways by which platelets are activated[90] and by which ischemic events can occur, it is unrealistic to expect any single drug to abolish all ischemic events.[101,102]

$P2Y_{12}$ RECEPTOR BLOCKING DRUGS

The Thienopyridines

Clopidogrel

Efficacy

Originally introduced as a safer drug than its precursor ticlopidine, clopidogrel has been shown to be marginally more effective than aspirin for the secondary prevention of vascular events.[103] Given its cost and side-effect profile, it should only be used as the primary drug for the prevention of cardiovascular events in patients who are intolerant or allergic to aspirin[23] or to provide enhanced protection when combined with aspirin[23] (albeit with an increased risk of bleeding[104]). Treatment should therefore be individualized based on guideline recommendations.[8–12,15,23,31,32,105–107]

Pharmacokinetics

Clopidogrel is a prodrug and has no direct antiplatelet activity of its own. After oral administration of clopidogrel, the drug is variably absorbed with approximately 50% bioavailability.[108] The majority of absorbed clopidogrel (85%) is extensively hydrolyzed by esterases to the inactive carboxylic acid metabolite SR 26334.[109] In the liver, clopidogrel is metabolized in a 2-step process by CYP3A4/3A5 with additional contributions by CYP2B6/1A2/2C9/2C19[110] to a very short-lived active metabolite (R130964), which is responsible for its effect on platelet aggregation.[111] This process demonstrates considerable interpatient variability,[112] and a genetic component to the variability is likely.[85] Recent investigations have identified that variants of the *CYP2C19* genotype (e.g., the loss of function *CYP2C19**2 allele[113]) are associated with diminished platelet response to clopidogrel[114,115] but this may be overcome by monitoring

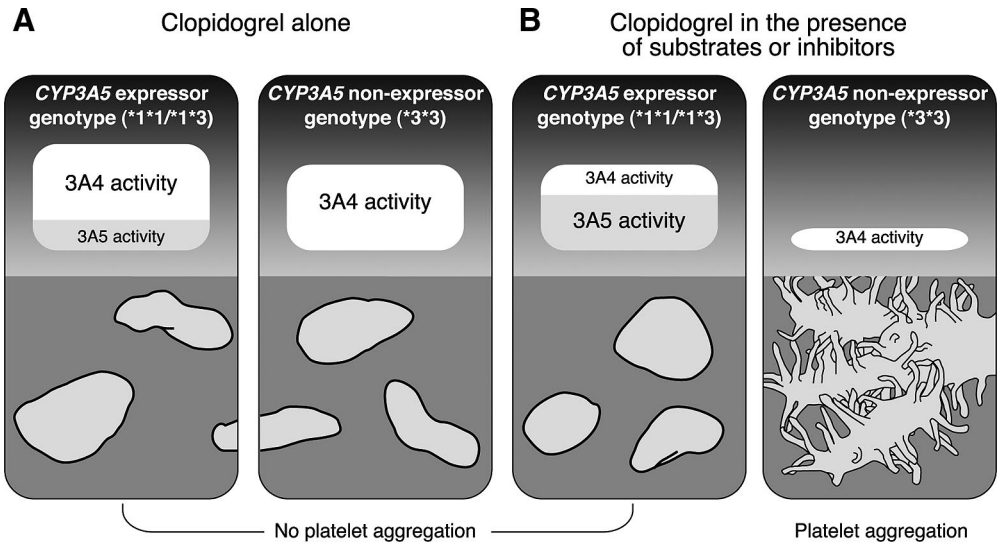

Figure 3. A, Cytochrome P450 (CYP) 3A4 and CYP3A5 are major isoforms of the CYP3A system. Total CYP3A activity accounts for 20% of all phase I reactions in the liver and metabolizes >50% of drugs. Under usual conditions, in which both CYP3A4 and CYP3A5 contribute to total CYP3A activity, CYP3A4 is probably the main contributor. Therefore, the antiplatelet activity of clopidogrel may not differ substantially between patients with the CYP3A5 expressor genotype and those with the nonexpressor genotype. B, In the presence of multiple substrates or inhibitors, CYP3A4 is more easily inhibited than CYP3A5, and therefore CYP3A5 becomes the main contributor to total CYP3A activity. In this condition, total CYP3A activity would differ depending on the patient's CYP3A5 genotype. (Photograph by Lianne Friesen and Nicholas Woolridge.) (From Suh et al.,[123] with permission.)

and adjusting the dose based on the platelet reactivity.[116] Peak concentrations of the parent drug, its active metabolite, and the carboxylic acid metabolite occur within approximately 1 to 2 hours[109,111] and there is little increased efficacy for doses >600 mg because of limited drug absorption.[117] The drug and its metabolite are extensively bound to serum proteins. Elimination is by the feces (50%) and urine (50%).[109] Dosage adjustment is generally not necessary in patients with renal[118] or hepatic[119] dysfunction. Inhibition of platelet aggregation reaches a level of approximately 40% to 60% after 3 to 7 days of daily administration of 75 mg, but this time can be significantly shortened by administering an initial loading dose.[120]

Pharmacodynamics

Significant interpatient variability in antithrombotic effects of clopidogrel has been ascribed to the variability in drug absorption as well as to alterations and genetic differences in hepatic metabolism.[108,113–115,121] Clopidogrel's active metabolite binds to the platelet $P2Y_{12}$ receptor to form disulfide bridges with the extracellular cysteine residues Cys17 and Cys270[122] to irreversibly inhibit adenosine diphosphate (ADP)-induced platelet aggregation.[123] The possibility of a rebound increase in platelet activity after discontinuation of clopidogrel therapy has been raised by a retrospective review demonstrating an increased incidence of death and AMI clustered in the 90 days after discontinuation of clopidogrel.[124] A subsequent prospective study could not confirm these results although the number of patients studied was small.[125] Until this issue is further clarified, it is suggested that care should be exercised when one is considering discontinuing clopidogrel before surgery.

Adverse Effects

The major side effect of clopidogrel administration is the increased risk of bleeding.[104] Use of clopidogrel in the perioperative period has been associated with an increased need for surgical reexploration for bleeding and use of blood products after cardiac surgery.[126] Use of a bleeding management algorithm was associated with a reduction in transfusion requirements after cardiac surgery in patients treated with clopidogrel, although the bleeding rate was still substantially higher than in a group of control patients not receiving clopidogrel.[127] A postoperative algorithm based on reintroduction of antiplatelet drugs when chest tube drainage was <50 mL/h allowed the successful reintroduction of aspirin and clopidogrel without an increased risk of bleeding.[128] The side-effect profile of clopidogrel necessitating early discontinuation because of side effects includes neutropenia, thrombocytopenia, or hemorrhagic events.[129] Compared with aspirin, there were fewer GI symptoms but an increased incidence of diarrhea and rash. A rare but significant complication of clopidogrel is the development of thrombotic thrombocytopenic purpura.[130]

Drug Interactions

Because of the requirement for metabolism of clopidogrel by CYP3A4/3A5 to generate the active metabolite, there is the potential for clinically significant drug interactions, which could lead to therapeutic failure.[111,131] CYP3A represents 40% to 80% of the cytochromes responsible for drug metabolism in humans,[132] although there is substantial variability. Clopidogrel is metabolized predominantly by the 3A4 allele; however, 3A5 may contribute as much as 50% of hepatic CYP3A activity. The antiplatelet efficacy of clopidogrel may be influenced by 3A5 functional polymorphism (Fig. 3).[123] There is concern that drugs that are CYP3A substrates (e.g., lipophilic statins) can inhibit the metabolism of clopidogrel to its active metabolite and thus lead to thrombosis.[131] Most studies have not demonstrated an increased risk for thrombosis in patients receiving both

CYP3A4 metabolized statins and clopidogrel.[133–136] However, there are significant limitations to the interpretation of the results (reviewed in Neubauer and Mugge[137]), and further study that accounts for confounders is required.

Clopidogrel activation to active metabolite is also dependent on metabolism by the CYP enzyme system.[110] Randomized clinical trials have demonstrated the ability of the PPIs to reduce the antiplatelet effect of clopidogrel[138,139] and large observational studies have, in general, demonstrated that the combination may lead to an increased mortality risk[140,141] or readmission for MI.[142] Given that PPIs are recommended for patients receiving antiplatelet drugs who have gastric irritation or bleeding,[143] and because they are frequently prophylactically administered in the perioperative period,[144,145] patients receiving this combination of drugs should be monitored closely.

Clopidogrel HPR and Resistance

HPR also occurs with clopidogrel administration.[61,146] As with aspirin, the consequences of inadequate clopidogrel effect on platelet reactivity can be devastating including MI, stroke, and death,[147] but in the absence of biochemical testing (Fig. 2) to establish whether HPR exists, clinical reports of clopidogrel "resistance"[148,149] should more appropriately be considered treatment failures.

The response to clopidogrel administration also has a bell-shaped curve and therefore a small percentage of patients would statistically be described as poor responders based on this phenomenon alone.[112] Many of the same factors leading to aspirin HPR apply also to clopidogrel HPR (Table 3). Clopidogrel treatment factors for nonresponse that have been identified that are unrelated to measurement of drug effect include noncompliance (the incidence of which may far outweigh any degree of pharmacological HPR[150]), inability to pay for or access the medication,[151] and inadequate education about the necessity of continuing the medication at the time of hospital discharge.[152] Nevertheless, depending on the assay used, a substantial proportion of patients (up to 31%[153]) who receive clopidogrel in the usual doses are reported to have an inadequate response in terms of antiplatelet activity[154] and a significant proportion of these can have adverse outcomes.[60] Intrinsic factors that affect the interaction of active metabolite with its receptors (such as genetic alterations in the *CYP2C19* gene, $P2Y_{12}$ receptor polymorphisms, or alterations in intracellular signaling mechanisms) may also be involved (Table 3).[155–157]

However, some patients have been demonstrated to have HPR in response to treatment with both aspirin and clopidogrel.[158] These patients seem to be at very high risk for drug-eluting stent (DES) thrombosis or death.[158] It should be noted, however, that although dual antiplatelet drug HPR may occur, HPR to one class of antiplatelet drugs does not necessarily confer HPR to other classes of antiplatelet drugs. Some nonresponders to a 300-mg initial loading dose of clopidogrel can be converted to responders by increasing the loading dose,[159] by increasing the maintenance dose,[160] or by increasing both the loading and maintenance dose.[161] The degree of platelet reactivity (and drug responsiveness) may differ depending on such things as body mass index,[116] stress,[162] and the timing of drug administration in relation to the degree of platelet reactivity during the inciting event such as PCI[153] or surgery.[163] Of note, diabetic patients seem to have a consistently high level of HPR when treated with thienopyridines.[164] As with aspirin, increased catecholamine levels have been identified as a risk factor for increased residual platelet reactivity despite dual antiplatelet therapy.[82,165] The perioperative period may therefore be a period of increased risk for thrombosis.[166] Until this question has been studied, in situations of high risk for thrombosis in which clopidogrel was discontinued before surgery, it may be reasonable to consider reinstitution of clopidogrel therapy with a bolus of 300 to 600 mg to reestablish adequate antiplatelet effects after adequate hemostasis has been ensured.[166] Antiplatelet therapy should also include the use of aspirin,[19] which should be reinstituted as soon as hemostasis has been achieved or on the morning after surgery.[35]

Prasugrel (CS-747, LY640315)

Prasugrel is one of several new drugs that also act at the $P2Y_{12}$ receptor[167] (Fig. 1) and has been introduced into practice for the prevention of thrombosis after PCI.[33] It belongs to the thienopyridine class of therapeutic drugs.[168]

Efficacy

Randomized clinical trials have established the efficacy of prasugrel as an antithrombotic drug.[169] In the setting of PCI, initial studies suggested that prasugrel produced a greater degree of platelet inhibition than clopidogrel and was associated with fewer incidences of major adverse cardiac events (MI, recurrent ischemia, and clinical target vessel thrombosis).[170,171] In a follow-up phase III study, patients undergoing PCI and receiving aspirin were randomized to receive either prasugrel 60 mg as an initial loading dose and then 10 mg daily (n = 6813) versus clopidogrel 300 mg loading dose and 75 mg (n = 6795) daily, and followed for 6 to 15 months.[172] Prasugrel administration was associated with a significant reduction in death from cardiovascular causes, nonfatal MI, or nonfatal stroke (9.9% vs 12.1%). In addition, prasugrel produced a significant reduction in the rates of MI (7.4% vs 9.7%), urgent target vessel revascularization (2.5% vs 3.7%), and stent thrombosis (1.1% vs 2.4%). However, there was an increased risk of bleeding events, particularly in patients older than 75 years of age, with a small body mass index, with a history of stroke or transient ischemic attack (TIA), and/or in those undergoing coronary artery bypass graft (CABG) surgery. Subgroup analysis of patients receiving coronary artery stents (either bare metal or DES) for ACS[173] or ST segment elevation MI[174] demonstrated improved protection from in-stent thrombosis (and subsequent death or MI) when prasugrel was given, without increased risk for major bleeding complications. Other subgroup analyses have shown greater protection using prasugrel in patients with diabetes mellitus[175] and a reduction in subsequent thrombotic events after the initial event.[176]

Pharmacokinetics

Animal studies have shown prasugrel to be 10 to 100 times more potent than clopidogrel in the inhibition of platelet

aggregation.[168] Similar to clopidogrel, prasugrel is a prodrug and must be metabolized to an active metabolite to exhibit its antiplatelet effect.[177] Conversion of prasugrel to its active metabolite is more rapid than clopidogrel, involving only a single cytochrome P450–dependent step (CYP3A4 and to a lesser extent CYP2B6),[178] leading to increased levels of the active metabolite and hence increased clinical effect.[179] Prasugrel metabolism seems to be less affected by genetic variations in CYP2C19 and CYP2C9 than clopidogrel[180] and less affected by drug interactions involving CYP3A4 for metabolism leading to less variation in active metabolite formation.[111] In healthy volunteers, prasugrel is rapidly absorbed and metabolized after oral administration with peak concentrations of the metabolites occurring at 0.5 hour.[181,182] Approximately 68% of a dose is excreted as metabolites in the urine and the remainder in the feces.[181] Dose-finding studies have shown maximum effects with an acceptable safety profile with an initial loading dose of 40 to 60 mg, and dose-dependent inhibition of platelet activity during maintenance dosing with a daily dose of 15 mg producing a sustained response.[183–185] The ratio of the active metabolite for prasugrel has been reported to be 2.2 times higher than that for clopidogrel after a loading dose, which may explain the faster onset of activity, higher levels of active compound, and reduced variability of platelet inhibition observed with prasugrel.[179]

Pharmacodynamics

In common with other thienopyridine derivatives, prasugrel's active metabolite (R-138727) irreversibly binds to the $P2Y_{12}$ receptor by forming disulfide bridges between extracellular cysteine residues at positions Cys17 and Cys270 to prevent platelet activation.[122] In patients with stable coronary artery disease, prasugrel produced a faster and more effective inhibition of platelet function than clopidogrel.[186,187] In multiple-dose studies, the maximum antiplatelet effect occurred after 2 days and recovery of platelet function occurred gradually over the 2 days after discontinuation of the drug.[168] In a study comparing platelet aggregation response to a loading dose of prasugrel 60 mg or clopidogrel 300 mg, the incidence of poor platelet aggregation response after prasugrel administration was lower (0%) than for clopidogrel (17%–43%).[188] When healthy subjects receiving clopidogrel therapy were switched directly to prasugrel (with or without a loading dose), greater inhibition of platelet aggregation was observed without an increased bleeding risk.[189] In patients with a demonstrated *CYP2C19*2* loss of function allele with reduced ability to generate the active metabolite of clopidogrel, use of prasugrel improved platelet function inhibition in patients for whom HPR was demonstrated using clopidogrel.[157]

Adverse Effects

The major adverse effect of prasugrel is bleeding. Prasugrel is a more potent inhibitor of platelet function than clopidogrel.[190] In the phase III trial, prasugrel administration was associated with a significantly increased incidence of major adverse bleeding events (2.4% vs 1.8%; hazard ratio, 1.32).[172] There was a higher incidence of life-threatening bleeding (1.4% vs 0.9%), including nonfatal bleeding (1.1% vs 0.9%) and fatal bleeding (0.4% vs 0.1%). Although it may be anticipated that excess bleeding might occur based on the increased potency of prasugrel, patients at risk for bleeding were excluded from the trial to start, prompting one editorialist to comment that more extended use of the drug in excluded patients would likely be associated with an even greater risk of bleeding.[191] He calculated a risk/benefit ratio of 1:1, i.e., for every additional life saved by the use of prasugrel over clopidogrel, one could expect an additional death due to bleeding. He noted in particular that patients with a history of stroke or TIA were particularly susceptible to the adverse bleeding risk (2.3% vs 0%) and suggested that, at the dose tested in this trial, prasugrel should be avoided in patients with known cerebrovascular disease. Subsequent analysis of bleeding events has determined that the majority occurred during the maintenance phase of the study and might be ameliorated in high-risk patients (age >75 years or weight <60 kg) by a reduction in the maintenance dose.[167,192]

Drug Interactions

Because of the requirement for metabolism by the cytochrome P450 system (CYP3A4/CYP2B6), there is a theoretical possibility of interactions with other drugs metabolized by that system although enzyme kinetic studies suggest this is unlikely.[139,178,193]

Prasugrel HPR

Compared with clopidogrel, use of prasugrel led to fewer nonresponders and better clinical response in diabetic patients.[164] Poor response to clopidogrel (as measured by light transmission aggregometry) was attributed to reductions in the amount of measured active metabolite available to interact with platelets as opposed to alterations in the platelet $P2Y_{12}$ receptor.

The place of prasugrel in the management of atherothrombotic occlusive disease remains to be determined. Further clinical trials are ongoing (e.g., TRILOGY-ACS, SWAP, ACAPULCO, OPTIMUS-3), examining the potential utility of prasugrel in a variety of other patient populations.[167] From a practical point of view, prasugrel is more potent than clopidogrel but not shorter acting so one could expect that in the perioperative period there may be an increased risk of bleeding. When, or if, it should be discontinued in the perioperative period has not been studied but discontinuance a minimum of 5 days before elective surgery where there is significant risk of bleeding would be in keeping with the guidelines suggested for clopidogrel and based on the pharmacokinetic/pharmacodynamic properties of the drug.[168,183,184]

Elinogrel (PRT060128)

Elinogrel is a direct-acting, reversible $P2Y_{12}$ receptor inhibitor with a novel structure (sulfonylurea) and can be administered both orally and IV.[194] This allows for the rapid onset of antiplatelet activity after IV administration and then a transition to a predictable platelet inhibition with the oral dosing form.[195]

Efficacy

Phase I studies demonstrated the ability to inhibit ADP-induced platelet aggregation within 20 minutes of administration; dose-dependent inhibition of platelet aggregation;

synergism when administered with aspirin; and additional inhibition of platelet aggregation in the Early Rapid Reversal of Platelet Thrombosis with IV Elinogrel before PCI to Optimize Reperfusion in Acute Myocardial Infarction (ERASE-MI) study. ERASE-MI was a phase IIA study in subjects undergoing primary PCI and randomized to receive either elinogrel or placebo before the start of the diagnostic angiogram that preceded the primary PCI procedure.[196] It was conducted in 2 phases: phase I was a dose-escalation study examining 10 mg (n = 10), or 20, 40, or 60 mg (n = 20 each) or placebo; phase II was a dose-confirmation study examining the highest tolerated dose but was not completed because the sponsor terminated the study for administrative reasons. Patients could receive aspirin, heparin, and clopidogrel but other anticoagulants were proscribed. No major bleeding events occurred in the treated population at any dose. No differences in adverse events were recorded although they were numerically higher in the placebo group. The authors concluded that elinogrel, at the doses examined in this study, was feasible and tolerable. The drug is undergoing further study (INNOVATE PCI NCT00751231).

Pharmacokinetics and Pharmacodynamics

After administration of a 50-mg oral dose, approximately 56% of the total dose was excreted in urine and 48% in feces. The main circulating compound was unchanged elinogrel and the major compound excreted in urine and feces was the parent compound. The major metabolic route was by demethylation to form the metabolite PRT060301 (approximately 10%).[194] In a study of 20 patients who had previously undergone PCI and were being treated chronically with clopidogrel 75 mg and aspirin 81 mg daily and screened for the presence of HPR, elinogrel 60 mg was given orally between 12 and 16 hours after the previous day's dose of clopidogrel.[197] The drug had a terminal elimination half-life of 12 hours and was cleared by the hepatic and renal routes with only limited metabolism.[197] Peak concentration was observed at 4 to 6 hours followed by a decrease to negligible levels by 24 hours. Plasma concentrations mirrored the pharmacodynamic effect. The antiplatelet effect peaked at 4 to 6 hours and returned to predosing levels by 24 hours. In patients for whom HPR was demonstrated while receiving aspirin and clopidogrel, additional inhibition of platelet aggregation after elinogrel administration occurred even in subjects known to have the *CYP2C19*2* allele.[194]

Adverse Effects

In the phase I clinical trials, single-dose elinogrel was well tolerated with no serious or clinically significant adverse events. In the phase IIa trial, the incidence of bleeding and serious adverse events was similar.[194] In theory, because of its sulfonylurea backbone, patients with a history of adverse reactions to sulfonylurea drugs might be at increased risk for development of allergic type reactions.

ADP RECEPTOR ANTAGONISTS

Cangrelor (AR-C69931)

Cangrelor is an ADP receptor antagonist that has been investigated in recent clinical trials[167,198] (Fig. 1).[33] Because it is a short-acting, IV, reversible inhibitor of platelet function, it has the potential to play a significant role in the management of patients with atherosclerotic disease in the perioperative period.

Efficacy

In small studies, cangrelor was an effective antithrombotic drug in patients with ACS, unstable angina, or non–Q wave MI.[199,200] In a randomized clinical trial of patients with AMI receiving cangrelor alone, alteplase alone, or 1 of 3 differing doses of cangrelor plus half-dose alteplase, cangrelor was an effective adjunct when added to alteplase for resolution of ST segment elevation.[201] The combination was better than either drug alone. Researchers of 2 phase III clinical trials using cangrelor in patients undergoing PCI have recently reported their outcomes. Bhatt et al.[202] performed a randomized trial of the addition of cangrelor or placebo to clopidogrel in 5362 patients undergoing PCI (CHAMPION PLATFORM Study). The primary end point was a composite of death, MI, or ischemia-driven revascularization at 48 hours. There was no difference in the primary end point between the 2 groups. In 2 prespecified subgroup analyses, cangrelor produced a significant difference in the rate of stent thrombosis and death from any cause. No differences in transfusion rate were observed although a higher incidence of groin hematoma occurred in the cangrelor-treated group. The trial was terminated early when an interim analysis concluded that the trial was unlikely to show superiority for the primary end point. The second trial examined the effect of cangrelor or clopidogrel administered to 8716 patients before undergoing PCI (CHAMPION PCI Trial).[203] The same composite end point was used as in the CHAMPION PLATFORM trial. Again, no difference in outcome was measured. This trial also was terminated early for lack of efficacy.

Pharmacokinetics

Given IV, cangrelor has a rapid onset of action (steady state at 30 minutes in the absence of a loading dose) and clearance (50 L/h) with an elimination half-time of <9 minutes. This leads to rapid return of platelet function (within 60 minutes) when the drug is discontinued.[204] Metabolism is by sequential dephosphorylation and there are no active metabolites.[167] The drug is metabolized in plasma and metabolism seems to be independent of abnormalities of liver or kidney function suggesting its utility in patients with impaired renal function.[167]

Pharmacodynamics

Cangrelor acts as a reversible inhibitor of the $P2Y_{12}$ receptor on the platelet surface.[205] It achieves greater inhibition of platelet aggregation than that obtained by clopidogrel.[206]

Adverse Effects

In early clinical trials, cangrelor was well tolerated (bleeding, transient increases in liver enzymes, and bleeding at injection sites were the most common side effects).[199–201,207] In patients undergoing PCI, cangrelor was not associated with an increased bleeding risk in patients receiving concomitant aspirin, heparin, and placebo for 18 to 24 hours, or, when compared with patients receiving abciximab before PCI, with an increased risk of bleeding or adverse cardiac events.[207] In the phase III

clinical trials, cangrelor administration was associated with trends toward increased bleeding.[202,203] Although the mechanism has not been determined, concern has been raised about the possibility of an increased incidence of dyspnea when drugs from this class are used.[208]

Drug Interactions

When given as combined therapy, cangrelor inhibited the antiplatelet activity of clopidogrel but not when clopidogrel was administered after cangrelor sequentially.[209] The mechanism was postulated to be due to inhibition by cangrelor of the binding of the active metabolite of clopidogrel to serine residues of the $P2Y_{12}$ receptor on the platelet surface.

An IV $P2Y_{12}$ inhibitor might well serve as an effective bridge to treatment in the perioperative period or in situations whereby operative intervention is a possibility, and research on the role cangrelor might have as bridge therapy for elective cardiac surgery is continuing. Such a drug would be an important advance in the safe management of patients requiring antiplatelet therapy in the perioperative period.

CYCLOPENTYLTRIAZOLOPYRIMIDINES

Ticagrelor (AZD6140)

Ticagrelor is an orally active reversible $P2Y_{12}$ receptor antagonist of the cyclopentyltriazolopyrimidine class of drugs undergoing clinical trials[167,210] (Fig. 1).[33]

Efficacy

Ticagrelor has been shown to rapidly and effectively inhibit platelet aggregation at doses ranging from 50 to 200 mg twice daily. On day 1, peak inhibition occurred at 2 to 4 hours whereas there was minimal inhibition demonstrated with clopidogrel (75 mg twice a day). For the subset of 84 patients requiring CABG surgery in a phase II dose-finding study of 2500 patients presenting with ACS,[211] there was no increased incidence of major bleeding in ticagrelor patients requiring surgery within 24 hours of drug administration overall (1 of 2 patients in the clopidogrel group versus 5 of 10 ticagrelor patients), but a tendency for reduced bleeding for patients requiring surgery between days 1 and 5 was observed. In the trial as a whole, there were more asymptomatic ventricular pauses observed in the ticagrelor-treated patients. No differences in death occurred, but there was a slight trend toward reduced incidence of MI in ticagrelor-treated patients.

Ticagrelor was subsequently evaluated in a phase III, double-blind, randomized clinical trial (Study of Platelet Inhibition and patient Outcomes [PLATO]) in patients with ACS.[212] Patients with ACS, with or without ST segment elevation, were randomized to receive ticagrelor 180-mg loading dose followed by 90 mg twice daily ($n = 9333$) or clopidogrel 300- to 600-mg loading dose followed by 75 mg daily ($n = 9291$) for the prevention of cardiovascular events. The primary end point (a composite end point of time to the earliest occurrence of MI, stroke, or death from vascular causes) occurred in significantly fewer patients when examined at the 12-month follow-up time point (ticagrelor 9.8% vs clopidogrel 11.7%; $P < 0.001$). For patients receiving a stent, the rate of stent thrombosis was significantly lower in the ticagrelor group (1.3% vs 1.9%; $P = 0.009$). No differences in the rate of major bleeding complications were observed (ticagrelor 11.6% vs clopidogrel 11.2%; $P = 0.43$). Analysis of the stroke subpopulation alone revealed an increased incidence of hemorrhagic stroke (0.2% vs 0.1%; $P = 0.10$). In the subpopulation of patients undergoing CABG surgery, no difference in the rate of major bleeding complications was observed (ticagrelor 7.4% [$n = 619$] vs clopidogrel 7.9% [$n = 654$]). An increased incidence of major or minor bleeding (16.1% vs 14.6%; $P = 0.008$), dyspnea requiring discontinuation of treatment (0.9% vs 0.1%; $P < 0.001$), ventricular pauses of >3 seconds within the first week of therapy (5.8% vs 3.6%; $P = 0.01$), and discontinuation as a result of any adverse event (7.4% vs 6.0%; $P < 0.001$) was observed in the study population as a whole. The authors concluded that ticagrelor was more effective than clopidogrel for the management of patients with ACS without an increased bleeding risk. An accompanying editorial suggested that, because of its reversible effect on platelet function, ticagrelor may have utility in patients for whom the coronary anatomy is unknown and in whom a CABG procedure is deemed probable.[213] In addition, for patients receiving prasugrel or clopidogrel and requiring elective surgery, switching them to ticagrelor 5 to 7 days before surgery could be considered. Caution with its use in patients with a history of stroke or TIA was advised. These recommendations require verification in properly conducted clinical trials. In a predefined subset of patients undergoing a planned invasive strategy, fewer patients randomized to the ticagrelor group had the composite outcome of cardiovascular death, MI, or stroke without an increased incidence of bleeding compared with the group randomized to clopidogrel treatment.[214] In a randomized, crossover study, use of ticagrelor produced increased platelet inhibition as compared with clopidogrel and more patients considered nonresponsive to clopidogrel[215] became responsive to ticagrelor than vice versa.

Pharmacokinetics

Ticagrelor is absorbed orally and does not require metabolic activation for its clinical effect.[216,217] It has one known active metabolite, which is present in blood at a concentration approximately one-third that of the parent compound as determined in phase I trials.[216,217] After oral dosing in healthy volunteers, peak effect on platelet inhibition was measured at 2 to 4 hours.[216] The drug seems to have linear kinetics[217] and after twice-daily administration of ticagrelor to patients with atherosclerotic disease, there was a linear and dose-related increase in ticagrelor and its active metabolite with no age- or gender-related differences.[216] The terminal half-life was approximately 7 hours.[217]

Pharmacodynamics

Ticagrelor binds to the $P2Y_{12}$ receptor in a reversible manner and nearly completely inhibits ADP-induced platelet aggregation.[216,218] It has a faster onset and offset of platelet inhibition than clopidogrel.[219] Ticagrelor has been shown to rapidly and effectively inhibit platelet aggregation at doses ranging from 50 to 200 mg twice daily.[216] Its ability to interact with the $P2Y_{12}$ receptor does not seem to be affected by alterations in single nucleotide polymorphisms of the receptor gene.[220] Ticagrelor produces more rapid and greater inhibition of platelet aggregation than

clopidogrel.[216,221] Doses >100 mg produced very little additional increase in the degree of inhibition of platelet aggregation. When compared with clopidogrel, no differences in inflammatory markers measured in a group of patients with ACS were detected.[222]

Adverse Effects

The most common adverse event after ticagrelor administration was bleeding.[216] Dyspnea requiring discontinuation of therapy occurred in a larger proportion of patients (0.9% ticagrelor vs 0.1% clopidogrel) in the PLATO trial.[212] In the ONSET/OFFSET study comparing ticagrelor ($n = 57$), clopidogrel ($n = 54$), or placebo ($n = 12$),[219] in patients with stable coronary artery disease, the incidence of dyspnea and effect on pulmonary function measured by pulmonary function studies were examined.[223] The incidence of dyspnea was 38.6% in ticagrelor-treated patients, 9.3% in the clopidogrel group, and 8.3% in the placebo group ($P < 0.001$). Dyspnea led to drug discontinuation in 3 patients in the ticagrelor group and was reversible. Dyspnea occurred early (within the first week) in the majority of affected patients and was described as mild. No changes in pulmonary function in any group were measured. Dyspnea was not a function of altered pharmacokinetic parameters.

PHOSPHODIESTERASE INHIBITORS

Dipyridamole

Dipyridamole is a pyrimidopyrimidine derivative with vasodilator and antiplatelet properties.[224]

Efficacy

Previous studies using the immediate-release formulation of dipyridamole did not, in general, show it to be superior to other antiplatelet drugs, and its side-effect profile (mainly headache) limited its application.[225] However, more recent guidelines now include aspirin and extended-release dipyridamole as an acceptable choice for the prevention of cerebral ischemic events in patients with noncardioembolic TIA or stroke.[3,4,105] Dipyridamole is inferior to clopidogrel treatment for aspirin-intolerant patients undergoing PCI and is not recommended for patients undergoing CABG surgery.[3] Aspirin continues to be the first choice for prevention of occlusive vascular disease followed by clopidogrel and cilostazol for certain populations.[3]

However, given the above recommendations and in particular for stroke management, it is likely that anesthesiologists will encounter patients receiving the combined therapy, i.e., aspirin and extended-release dipyridamole. Perioperative management should weigh the risks and benefits including the possibility of increased risk of bleeding caused by the combination.

Pharmacokinetics

Absorption of oral doses of dipyridamole is quite variable[226,227] but a modified-release formulation has improved the bioavailability.[228] The drug is metabolized to a glucuronide, excreted primarily in bile, and subject to enterohepatic recirculation with a terminal half-life of 19 hours making twice-daily dosage possible particularly when the modified-release formulation is used.[229] Dipyridamole is highly protein bound to albumin and α_1-acid glycoprotein,[230] with consequent reduction in drug effect.[231] Because α_1-acid glycoprotein is an acute phase reactant whose levels increase in the perioperative period,[232] there is a possibility of reduced drug effect because of increased protein binding if dosing is not increased.

Pharmacodynamics

The mechanism of action is thought to be via increased cyclic adenosine monophosphate (cAMP) by inhibition of nucleotide phosphodiesterase, blockade of the uptake of adenosine thereby increasing the amount of adenosine at the platelet vascular interface,[227] or direct stimulation of prostacyclin release from the endothelium.[227] In high doses, drug-induced vasodilation and tachycardia may produce myocardial ischemia, which may be a limiting factor for its use as an antiplatelet drug.[233] Compared with aspirin or clopidogrel, dipyridamole produced sustained platelet inhibition but via a broader range of mechanisms.[234,235]

Adverse Effects

Use of dipyridamole is associated with an increased risk of bleeding events.[47] The most common adverse effect of chronic administration is headache.[236] Dipyridamole has been used for cardiac diagnostic testing including stress echocardiograms (single-dose studies) and in that population there is a small incidence of death (0.9:10,000), stroke or TIA (1.22:10,000), AMI (1.76:10,000), bronchospasm (1.22:10,000), and arrhythmias (0.81:10,000) detected.[237]

Drug Interactions

When coadministered with aspirin, there is an increased risk for bleeding.[47] Although we could find no substantiating reports, it is possible that there could be additive hypotensive effects if dipyridamole was administered with other drugs that are vasodilators, e.g., ACE inhibitors.

Cilostazol

Cilostazol is a phosphodiesterase 3 inhibitor with vasodilator and antiplatelet aggregation properties[238] (Fig. 1).[33]

Efficacy

Cilostazol has been demonstrated to be effective in the setting of peripheral vascular disease[239] and is currently recommended for patients with moderate-to-severe disabling intermittent claudication who do not respond to exercise therapy, and who are not candidates for surgical or catheter-based interventions.[31] Cilostazol has been shown to prevent stent thrombosis and restenosis.[240,241] An enhanced antiplatelet effect of triple therapy (with aspirin and clopidogrel) has been demonstrated,[242] although side effects with cilostazol (skin rash and GI upset) limited its use.[243,244] For the prevention of stroke, Gotoh et al.[245] demonstrated a significant reduction in recurrence of cerebral infarction as compared with placebo alone. In a randomized trial examining the relative merits of cilostazol versus aspirin in patients with an ischemic stroke using as the primary outcome the recurrence of stroke, Huang et al.[246] determined that there was no difference in the ischemic stroke reoccurrence rate but patients treated with cilostazol had lower rates of cerebral bleeding suggesting perhaps an improved safety profile. Compared with aspirin alone, cilostazol and aspirin

demonstrated enhanced antiplatelet activity in patients undergoing off-pump coronary artery surgery.[247]

Pharmacokinetics

There is large variability in the absorption of orally administered cilostazol[248] that does not seem to be attributable to the activity of the drug transporter P-glycoprotein.[249] The drug is metabolized primarily by CYP3A4/5 with a lesser contribution by CYP2C19 to inactive metabolites.[250] It is extensively protein bound (approximately 95% primarily to albumin).[251] The elimination half-time for cilostazol is approximately 10 hours.[252] No differences in pharmacokinetics were detected based on age or gender in healthy subjects aged 50 to 80 years.[251,252] Although the clearance of cilostazol was increased in patients with renal failure[253] and decreased in patients with liver failure,[252,254] no dosage adjustments were necessary.

Pharmacodynamics

Cilostazol is a more potent inhibitor of platelet aggregation than ticlopidine or aspirin.[255] Its mechanism of action is to inhibit the intracellular enzyme phosphodiesterase 3 leading to an increase in cyclic adenosine monophosphate with resultant decreases in platelet aggregation and vasodilation.[252] Similar concerns about producing hypotension and tachycardia as a result of vasodilation as are present with dipyridamole are also relevant here.[256]

Adverse Effects

Headache is a common side effect of treatment with cilostazol and may be a reason some patients discontinue therapy.[257] In a postregistration placebo-controlled, randomized, double-blind safety trial of the use of cilostazol in patients with peripheral vascular disease, a significant proportion of patients discontinued therapy (60%).[258] There was no increased incidence of death or bleeding. A blinded post hoc analysis demonstrated an increased risk of cerebral vascular events in patients in the placebo arm (6.1% vs 3.2%).[259]

Drug Interactions

Because of its metabolism by CYP3A4 and CYP2C19, cilostazol may be involved in drug interactions with drugs also requiring these isoforms for their metabolism. Cilostazol metabolism was inhibited by omeprazole (a CYP2C19 inhibitor) and erythromycin (a potent inhibitor of CYP3A4) with resultant decreases in plasma concentrations of cilostazol and its active metabolite.[260,261] Coadministration with lovastatin (a CYP3A4 substrate) resulted in reductions in cilostazol plasma concentrations but not to clinically significant levels.[262] Lovastatin levels were increased but not to levels requiring dosage adjustments. There were no reports of a clinically significant interaction when coadministered with aspirin.[252]

PERIOPERATIVE MANAGEMENT

Antiplatelet drugs may increase the risk of surgical bleeding. However, there have been several reports of stent thrombosis and death in the perioperative period when antiplatelet drugs were discontinued.[34] In addition, increased mortality when surgery is delayed in patients taking antiplatelet drugs to allow coagulation variables to normalize has been reported.[263] These reports have raised concern about the appropriate management of antiplatelet drugs in the perioperative period.[264] The most appropriate timing of surgery after insertion of a bare metal stent or DES is still under active investigation but initial reports suggest that surgery within the first 3 months after insertion of either type of stent is particularly hazardous.[34,265] Thereafter, problems with late stent thrombosis are more prevalent in patients receiving DESs.[266] Although there seems to be no time frame when the risk becomes zero regardless of when a DES was inserted,[267] recent data suggest that the benefit of continuing dual antiplatelet therapy beyond 12 months is marginal.[268]

As a consequence of these concerns, the American Heart Association has released a statement[13] concerning premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents. This advisory comments that stent thrombosis is a catastrophic event with the incidence of death between 20% and 45% or MI up to 64%. It may be more common than previously appreciated particularly because there is increasing usage of these stents in patients with more complicated disease than those who were originally studied (so-called "off label" usage).[269] Although there were few data upon which to make any recommendation, the American Heart Association advisory observed that the objective evidence for an increased risk of bleeding during noncardiac surgery in patients with dual antiplatelet therapy continued perioperatively was weak. However, a recent report suggests that as many as 26% of patients will require noncardiac surgery within 5 years after PCI and, of these, 8.6% will have a bleeding episode.[270] These data suggest that as the use of antiplatelet therapy after DES continues and more patients receiving them present for elective surgery, there will be an increased risk for adverse bleeding outcomes in this population. The general experience with cardiac surgery is that there are increased bleeding complications when clopidogrel is part of dual antiplatelet therapy that is continued into the perioperative period.[17,18,271,272] Where possible, aspirin should be continued throughout the perioperative period. The advisory panel could find no satisfactory "bridge" therapy for stent patients during this period because anticoagulants had been determined to be unsatisfactory in this regard and led to increased bleeding. There were no data supporting the efficacy of glycoprotein IIb/IIIa drugs in this situation. They suggested that, in keeping with the advice given by a recent Food and Drug Administration panel[a] for all patients receiving DES, dual antiplatelet therapy should be continued for 12 months after stent insertion. (Support for this recommendation has been provided in a study that demonstrated that clopidogrel use for >1 year was associated with a lower mortality in patients having PCI and stent placement.[273]) The panel also made additional recommendations concerning the management of patients receiving a DES. These were as follows:

1. "Before implantation of a stent, the physician should discuss the need for dual antiplatelet therapy. In patients not expected to comply with 12 months of

[a]United States Food and Drug Administration Circulatory System Devices Panel. Available at: http://www.fda.gov/ohrms/dockets/ac/cdrh06.html#circulatory. Last accessed November 19, 2010.

thienopyridine therapy, whether for economic or other reasons, strong consideration should be given to avoiding a drug-eluting stent (DES).
2. In patients who are undergoing preparation for percutaneous coronary intervention and are likely to require invasive or surgical procedures within 12 months, consideration should be given to implantation of a bare-metal stent or performance of balloon angioplasty with provisional stent implantation instead of the routine use of DES.
3. A greater effort by healthcare professionals must be made before patient discharge to ensure patients are properly and thoroughly educated about the reasons they are prescribed thienopyridines and the significant risks associated with prematurely discontinuing such therapy.
4. Patients should be specifically instructed before hospital discharge to contact their treating cardiologist before stopping any antiplatelet therapy, even if instructed to stop such therapy by another healthcare provider.
5. Healthcare providers who perform invasive or surgical procedures and are concerned about periprocedural and postprocedural bleeding must be made aware of the potentially catastrophic risks of premature discontinuation of thienopyridine therapy. Such professionals who perform these procedures should contact the patient's cardiologist if issues regarding the patient's antiplatelet therapy are unclear to discuss optimal patient management strategy.
6. Elective procedures for which there is significant risk of perioperative or postoperative bleeding should be deferred until patients have completed an appropriate course of thienopyridine therapy (12 months after DES implantation if they are not at high risk of bleeding and a minimum of 1 month for bare-metal stent implantation).
7. For patients treated with DES who are to undergo subsequent procedures that mandate discontinuation of thienopyridine therapy, aspirin should be continued if at all possible and the thienopyridine restarted as soon as possible after the procedure because of concerns about late-stent thrombosis.
8. The healthcare industry, insurers, the US Congress, and the pharmaceutical industry should ensure that issues such as drug cost do not cause patients to prematurely discontinue thienopyridine therapy and to thus incur catastrophic cardiovascular complications."

Clearly, these recommendations have significant implications for anesthesiologists who manage patients during the perioperative period and will require appropriate consultation with surgeons and cardiologists as well as a clear understanding of the risk-benefit ratio for performance of procedures such as regional blocks, epidurals, and spinals.[274] Given that all new antiplatelet drugs will be required to be at least as effective as clopidogrel and the current recommendations against the performance of regional anesthesia when clopidogrel is present,[275] we suggest that, where possible, regional anesthesia should only be performed when it is certain that the return of adequate platelet function has been ascertained (Table 1). Although their value as monitors of drug effect continues to evolve,[276–279] this may be a place for the use of platelet function monitors in the perioperative period. Catheters placed perioperatively should be removed before reinstitution of antiplatelet therapy.

The Society for Cardiovascular Angiography and Interventions Drug-eluting Stent Task Force have also released their recommendations.[280] They provide "practical advice" on a number of related issues such as patient selection, stent implantation, and medical-legal concerns. Of most relevance to anesthesiologists is the section on dual antiplatelet therapy. They concur with the Food and Drug Administration panel recommendation to increase the duration of dual antiplatelet therapy to 12 months from 3 months for patients receiving DESs. Furthermore, despite a lack of conclusive evidence, they suggest that patients in whom stent thrombosis may be catastrophic or lethal should undergo platelet aggregation studies and where appropriate, the dose of clopidogrel should be increased to 150 mg/d when platelet aggregation studies show <50% inhibition (a study in patients with type 2 diabetes mellitus lends some strength to this recommendation[281]). They found no evidence that patients who have completed or discontinued their course of dual antiplatelet therapy, without incident, should restart thienopyridine therapy, although they should continue taking aspirin indefinitely. They reiterated that there are no proven "bridging" therapies for patients who must discontinue dual antiplatelet therapy for surgery.

Recognizing that cardiac surgery is associated with generation of an inflammatory response leading to increased platelet activation[81,83] and turnover[86] with resultant HPR for both aspirin and clopidogrel,[20,88,166] the following approaches should be considered:

- Aspirin therapy should be continued preoperatively and throughout the perioperative period[26] unless the risk of bleeding is considered to be high or the consequences of bleeding are significant, e.g., ophthalmological surgery.[35]
- Although there are currently no satisfactory risk stratification schemes with respect to the management of bleeding risk in patients taking antiplatelet drugs in the perioperative period,[282] patients undergoing urological surgery, major vascular surgery, cardiac surgery with identified risk factors,[283] neurosurgery involving the brain or spinal cord, or where the complications of bleeding might be catastrophic, e.g., ophthalmic surgery, clopidogrel should be discontinued 5 days preoperatively.[10,19]
- In patients at high risk of thrombotic complications (e.g., those with a DES in place), use of a higher dose of aspirin (e.g., 325 mg) in the postoperative period should be considered[19,94] with a return to a dose of 81 mg daily after 30 days.[88]Using a variety of tests of platelet function, Golański et al.[88] demonstrated that 37.5% of patients receiving 325 mg of aspirin after cardiac surgery were responders at day 10 postoperatively, increasing to a 96% response rate at 30 days, which forms the basis for this recommendation. In the postoperative period for patients at high risk of thrombotic complications (e.g., those with a DES in

Table 4. Comparison of Guideline Recommendations Regarding Antiplatelet Therapy in the Perioperative Period

	Reference document	Aspirin recommendation for preoperative management	Clopidogrel recommendation for preoperative management	Aspirin recommendation for postoperative management	Clopidogrel recommendation for postoperative management	Routine use of platelet function monitoring
American College of Chest Physicians	Douketis et al.[282]	Stop 7–10 d for patients *not* at high risk for cardiac events. For elective CABG or high-risk noncardiac surgery patients (exclusive of coronary stents), continue aspirin up to and beyond the time of surgery. If aspirin is interrupted, it should be restarted 6–48 h after CABG. In BMS patients within 6 wk of stent placement, or DES patients within 12 mo of stent placement, continue aspirin in the perioperative period	Stop 7–10 d for patients *not* at high risk for cardiac events. For elective CABG or high-risk noncardiac surgery patients (exclusive of coronary stents), stop clopidogrel at least 5 d, and preferably, within 10 d of surgery. In BMS patients within 6 wk of stent placement, or DES patients within 12 mo of stent placement, continue clopidogrel in the perioperative period	Start 24 h postoperatively for patients *not* at high risk for cardiac events (or the next morning) when adequate hemostasis has been achieved. For patients at high risk for cardiac event, or undergoing CABG, or with stent placement, continue throughout perioperative period (see preoperative recommendations). No dosing recommendation	Start 24 h postoperatively for patients *not* at high risk for cardiac events (or the next morning) when adequate hemostasis has been achieved. For patients at high risk for cardiac event, or undergoing CABG, or with stent placement, continue throughout perioperative period (see preoperative recommendations). No dosing recommendation	No
European Association of Cardiothoracic Surgery	Dunning et al.[19]	Stop 2–10 d for elective cardiac surgery. For ACS, continue until day of surgery	Stop 5–7 d for urgent cardiac surgery	Start 150–325 mg (325 mg preferred) within 24 h (preferably within 6 h) of cardiac surgery and continued for 1 y	Start clopidogrel 75 mg acceptable alternative to aspirin for graft patency. For patients having CABG for ACS, clopidogrel administration for 9–12 mo should be considered. For patients having cardiac surgery with a stent in situ, clopidogrel should be continued if the stented vessel has not been grafted	Thromboelastography
American College of Cardiology/ American Heart Association	Refs. 8, 10, 13, and 106	In DES patients who must undergo urgent surgery that mandates discontinuation of thienopyridine therapy, it is reasonable to continue aspirin if at all possible and restart thienopyridine as soon as possible.[13,106] Elective noncardiac surgery is not recommended within 4–6 wk of bare-metal coronary stent implantation in patients in whom thienopyridine or aspirin and thienopyridine therapy will need to be discontinued perioperatively.[106] For ACS/ NSTEMI patients for CABG, continue aspirin[10]	For ACS/NSTEMI patients for CABG as a postangiography management strategy: discontinue clopidogrel 5–7 d before elective CABG.[8,10] Elective procedures for which there is significant risk of perioperative or postoperative bleeding should be deferred until patients have completed an appropriate course of thienopyridine therapy (12 mo after DES implantation and a minimum of 1 mo for BMS implantation)[13]	Recommence as soon as possible. For patients with DES, consider dual therapy for 1 y	Recommence as soon as possible. For patients with DES, consider dual therapy for 1 y	None given

(Continued)

Table 4. *(Continued)*

Reference document	Aspirin recommendation for preoperative management	Clopidogrel recommendation for preoperative management	Aspirin recommendation for postoperative management	Clopidogrel recommendation for postoperative management	Routine use of platelet function monitoring
Present article	Assess risk of bleeding. Continue throughout perioperative period if possible	Assess risk of bleeding. If necessary, discontinue 5 d preoperatively	Assess thrombotic risk. If high and aspirin discontinued preoperatively, initiate aspirin 325 mg daily for 30 d then step down to 81 mg daily	Assess thrombotic risk. If high and clopidogrel discontinued preoperatively, give 1 initial postoperative dose of 300–600 mg and reinitiate maintenance therapy at 150 mg daily for 30 d then step down to 75 mg daily	Perhaps in certain clinical situations such as to assess compliance and timing of drug initiation

BMS = bare metal stent; DES = drug-eluting stent; ACS = acute coronary syndrome; NSTEMI = non-ST-segment elevation myocardial infarction; CABG = coronary artery bypass graft.

place) receiving clopidogrel, when the drug has been discontinued for ≥5 days in the perioperative period and there are no signs of ongoing bleeding, consideration should be given to rebolusing the drug (300–600 mg) with use of a higher maintenance dose (150 mg) for 30 days.[166,284]

- Resumption and continuation of other standard medical therapies including ACE inhibitors, statins, β-blockers, etc., should be initiated as soon as possible in the postoperative period.[285]

It should be recognized that these suggestions differ slightly from recently released guidelines primarily by suggesting clopidogrel discontinuation at 5 days before surgery (as opposed to 7–10 days),[282,286] and the use of rebolusing and higher maintenance doses postoperatively[19,35,282] (Table 4). There is a lack of uniformity in the guideline recommendations (e.g., when [or if] aspirin should be discontinued preoperatively, when clopidogrel should be discontinued preoperatively, when aspirin therapy should be reinitiated postoperatively and at what dose, when clopidogrel therapy should be reinitiated and at what dose, the duration of antiplatelet therapy postoperatively, and the role of platelet function monitors[19,282]), no doubt a reflection of the rapidly advancing knowledge base upon which recommendations can be made.

Bleeding: Prevention and Management of Complications

Although the degree to which antiplatelet therapy continuation contributes to transfusion requirements intraoperatively is uncertain,[287,288] it has to be acknowledged that continuing antiplatelet therapy in the perioperative period is not without risk for bleeding complications,[17,26,271,289] including after performance of regional anesthesia,[290,291] suggesting that an individualized approach to management of antiplatelet therapy is prudent. Guidelines on the management of antiplatelet therapy before cardiac surgery have been published.[19,292] Continued use of clopidogrel may lead to more blood product usage and need for surgical reexploration,[19] each of which carries additional risk for the patient.[293–296] Similarly, continued use of aspirin may lead to increased risk for transfusion and surgical reexploration.[19] Use of point-of-care platelet function monitors or standard platelet aggregometry may allow one to determine the degree of residual drug effect and therefore the ability to make an informed decision about the safety of performing regional anesthesia. The merits of each platelet function test to measure drug effect on platelet activity have been reviewed elsewhere and will not be further considered here.[297] If the performance of regional anesthesia is considered essential, platelet administration could be guided by platelet function monitoring if available.[298] Other potential perioperative uses of platelet function monitoring include evaluation of patient compliance, timing of surgery, identification of "hyper-responders" for whom continuation of aspirin or clopidogrel in the perioperative period might lead to an increased risk of bleeding, and as part of a transfusion algorithm to guide blood component administration.[64,127,299–302]

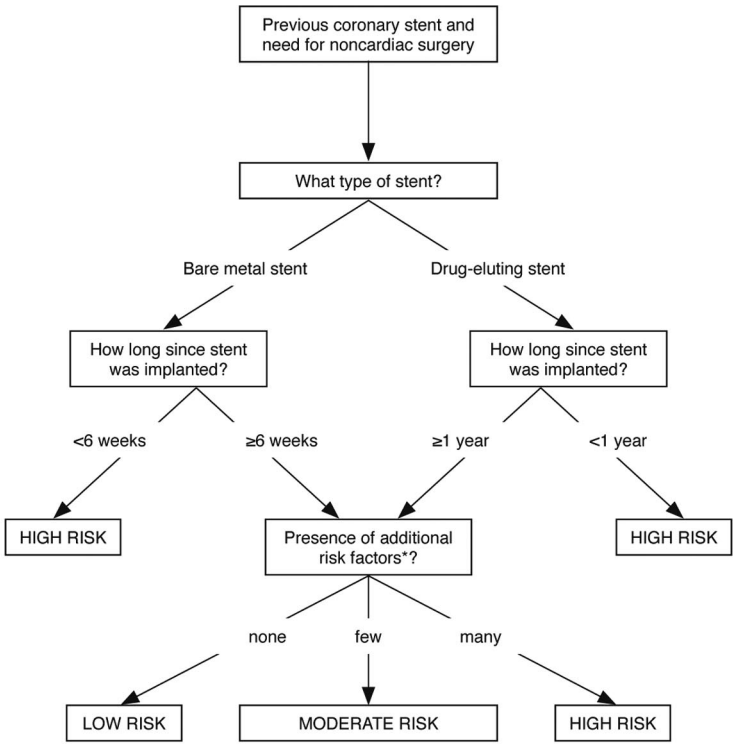

Figure 4. Flow chart to determine the risk of stent thrombosis. *N.B.* It is also essential to determine the level of compliance with antiplatelet medication administration when assessing risk. (From Riddell et al.,[316] with permission.)

***Additional risk factors for stent thrombosis**

Coronary anatomy	Stent-Indication	Patient
Bifurcation stenting	Acute coronary syndrome	Diabetes
Ostial stenting		Renal impairment
Small (<3.0 m) stent diameter		Advanced age
Long (>18mm) stent length		Low ejection fraction
Overlapping stents		Prior brachytherapy
Multiple stents		
Suboptimal result		

As regards the intraoperative management, in addition to component blood therapy including platelets, a meta-analysis has determined that the combined use of aspirin and antifibrinolytics did not increase prothrombotic complications and suggests that antifibrinolytics may reduce bleeding complications and have a role in the management of bleeding risk in high-risk patients receiving antiplatelet drugs perioperatively.[303] The merits of which antifibrinolytic drug is best given their risk and benefits continue to be debated[304–307] and are beyond the scope of this review. There may be merit in using point-of-care devices to reduce transfusion requirements and guide component therapy.[308–312] When hemorrhage is severe and unresponsive to conventional treatment, recombinant activated factor VII may be considered, although the possibility of increased thrombotic complications must also be considered, especially in patients with vascular disease.[19,313–315]

An Approach to Management

To help determine the best approach to the management of patients in the perioperative period, Riddell et al. have provided some advice based on consensus opinion.[316] The first step is to determine the risk of bleeding (not only the quantity but also the site, e.g., ophthalmological surgery) in consultation with the surgeon and cardiologist. The next step is to determine the risk of stent thrombosis (Fig. 4).[316] Finally, by assessing both risks, recommendations as to what to do with oral antiplatelet drugs are provided (Table 5).[316]

CONCLUSIONS

We have reviewed some of the issues of concern regarding the use of antiplatelet drugs in the perioperative period. In general, the safest approach to prevent thrombosis seems to be continuation of these drugs throughout the perioperative period except when concerns about perioperative bleeding outweigh those associated with the development of thrombotic occlusion. In situations in which a large inflammatory response is expected, higher doses or use of dual antiplatelet therapy may be indicated. Aspirin and clopidogrel (alone and in combination) have been the most studied and have the best-known risk-benefit profiles of drugs currently available. Other drugs, e.g.,

Table 5. Assessing the Risk of Surgery and Possible Stent Thrombosis

Risk of stent thrombosis	Risk of surgical bleeding		
	High	Moderate	Low
High	Stop all OADs Consider short-acting IV antiplatelet drugs while off OADs Proceed with surgery Restart OADs as soon as possible after surgery	Continue at least 1 OAD if possible Consider short-acting IV antiplatelet agents while off OADs Proceed with surgery Restart OADs as soon as possible after surgery	Continue all OADs Proceed with surgery
Moderate	Stop all OADs Proceed with surgery Restart OADs as soon as possible after surgery	Continue 1 OAD if possible Proceed with surgery Restart OADs as soon as possible after surgery	Continue all OADs Proceed with surgery
Low	Stop all OADs Proceed with surgery Restart OADs as soon as possible after surgery	Stop all OADs Proceed with surgery Restart OADs as soon as possible after surgery	Continue 1 OAD if possible Proceed with surgery Restart OADs as soon as possible after surgery

OAD = oral antiplatelet drug.
N.B. Where possible, compliance should be checked and appropriate platelet function tests performed.
Modified from Riddell et al.,[316] with permission.

prasugrel, dipyridamole, and cilostazol, have not been as extensively investigated. Whether drugs such as cangrelor and ticagrelor confer additional benefits remains to be established. Knowledge of the pharmacodynamics and pharmacokinetics may allow practitioners to anticipate difficulties associated with drug withdrawal and administration in the perioperative period including the potential for drug interactions.

DISCLOSURES

Name: Richard Hall, MD, FRCPC, FCCP
Conflicts of Interest: Dr. Hall has previously received honoraria from Bayer, Eisai, and Eli Lilly (makers of pharmaceutical agents referred to in this article).
Name: C. David Mazer, MD, FRCPC
Conflicts of Interest: Dr. Mazer has previously received honoraria from Bayer, AstraZeneca, and Bristol-Myers Squibb (makers of pharmaceutical agents referred to in this article).

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