Platelet $P2Y_{12}$ Receptor Inhibition and Perioperative Patient Management

Michael Mazzeffi, M.D., Kenichi A. Tanaka, M.D., Paul A. Gurbel, M.D., Udaya S. Tantry, Ph.D., Jerrold H. Levy, M.D.

The increasing use of antiplatelet drugs includes the administration of clopidogrel, ticagrelor, prasugrel, and cangrelor, drugs that inhibit the $P2Y_{12}$ receptor and are frequently used as part of dual antiplatelet therapy. New-generation drug-eluting stents are the standard of care for percutaneous coronary intervention (PCI), except in patients who cannot tolerate or are unlikely to adhere to dual antiplatelet therapy.[1] After PCI with a drug-eluting stent, dual antiplatelet therapy is recommended to reduce in-stent thrombosis and the risk of myocardial infarction.[2] For patients with a drug-eluting stent placed for acute coronary syndrome, 12 months of dual antiplatelet therapy is recommended.[2] For those with stable ischemic heart disease, dual antiplatelet therapy duration can be reduced to 6 months.[2]

Patients taking $P2Y_{12}$ receptor inhibitors frequently present for surgical procedures and have increased risk for perioperative bleeding when there is not adequate drug-withholding time before surgery. Individual $P2Y_{12}$ receptor inhibitor drugs have different potency and pharmacokinetics. For this reason, bleeding risk and reversal strategies differ somewhat by drug. In this clinically focused review, the authors discuss $P2Y_{12}$ receptor inhibitor drugs, their pharmacology, monitoring, appropriate withholding before elective surgery, and reversal strategies for patients who require urgent or emergent surgery.

$P2Y_{12}$ Receptor Inhibitor Pharmacology

The platelet $P2Y_{12}$ receptor is a purinergic G-protein–coupled receptor with seven transmembrane α-helices (342 amino acids; fig. 1).[3–5] Approximately 500 to 600 $P2Y_{12}$ receptors are expressed constitutively on a platelet's surface.[6] Binding of the $P2Y_{12}$ receptor with its agonist, adenosine diphosphate (ADP), triggers intracellular signaling *via* the Gi2α subunit coupled to the $P2Y_{12}$ receptor.[3] The latter interaction is followed by suppression of adenylyl cyclase activity and inhibition of cyclic adenosine monophosphate (AMP)–dependent protein kinase–mediated vasodilator-stimulated phosphoprotein phosphorylation.[3] Vasodilator-stimulated phosphoprotein inhibition is associated with a conformational change and activation of the glycoprotein (GP) IIb/IIIa receptor.[3] As a marker of $P2Y_{12}$ receptor signaling, vasodilator-stimulated phosphoprotein phosphorylation is used to monitor the antiplatelet response to $P2Y_{12}$ receptor blockers.

It has been proposed that reducing cyclic AMP by Giα-associated inhibition of adenylyl cyclase activity alone is insufficient to support normal platelet aggregation. Downstream signaling through the βγ subunit by phosphoinositide 3-kinase activation and the Rap1–guanosine triphosphate–interacting adaptor molecule/talin pathway is also important in promoting platelet aggregation.[7] Platelets are activated by multiple agonists including ADP, collagen, thromboxane, and thrombin. Sustained $P2Y_{12}$ receptor–mediated activation of the GPIIB/IIIa receptor appears to be one of the most important factors for stable platelet aggregation and is synergistic with thrombin induced platelet aggregation.[7,8] Based on the demonstration of the cumulative antithrombotic effects of aspirin and clopidogrel, the ADP–$P2Y_{12}$ receptor and thromboxane A_2–thromboxane receptor pathways are also synergistic.[3] Other mechanisms that activate platelets directly or indirectly through $P2Y_{12}$ include dense and α-granule release and P-selectin expression on platelet surfaces.[7]

During platelet aggregation, activated GPIIb/IIIa binds to fibrinogen, fibrin, and von Willebrand factor. As a comparison, approximately 80,000 GPIIb/IIIa receptors are expressed on an activated platelet's surface.[9] Limited and platelet-specific expression of $P2Y_{12}$ makes it an ideal target for antithrombotic therapy.[10] Although the $P2Y_{12}$ receptor was not well characterized until 2001, its importance was demonstrated as early as 1962 in a landmark study by Born[11] in which he concluded that "If it can be shown that ADP takes part in the aggregation of platelets in blood vessels, it is conceivable that AMP or some other substance

This article has been selected for the ANESTHESIOLOGY CME Program (www.asahq.org/JCME2025JAN). Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

Submitted for publication May 13, 2024. Accepted for publication July 8, 2024. Published online first on October 11, 2024.

Michael Mazzeffi, M.D.: University of Virginia School of Medicine, Department of Anesthesiology, Charlottesville, Virginia.

Kenichi A Tanaka, M.D.: Oklahoma University School of Medicine, Department of Anesthesiology, Oklahoma City, Oklahoma.

Paul A. Gurbel, M.D.: Sinai Center for Thrombosis Research and Drug Development, Sinai Hospital of Baltimore, Baltimore, Maryland.

Udaya S. Tantry, Ph.D.: Sinai Center for Thrombosis Research and Drug Development, Sinai Hospital of Baltimore, Baltimore, Maryland.

Jerrold H. Levy, M.D.: Duke University School of Medicine, Department of Anesthesiology, Durham, North Carolina.

 ANESTHESIOLOGY 2025; 142:202–16. DOI: 10.1097/ALN.0000000000005148

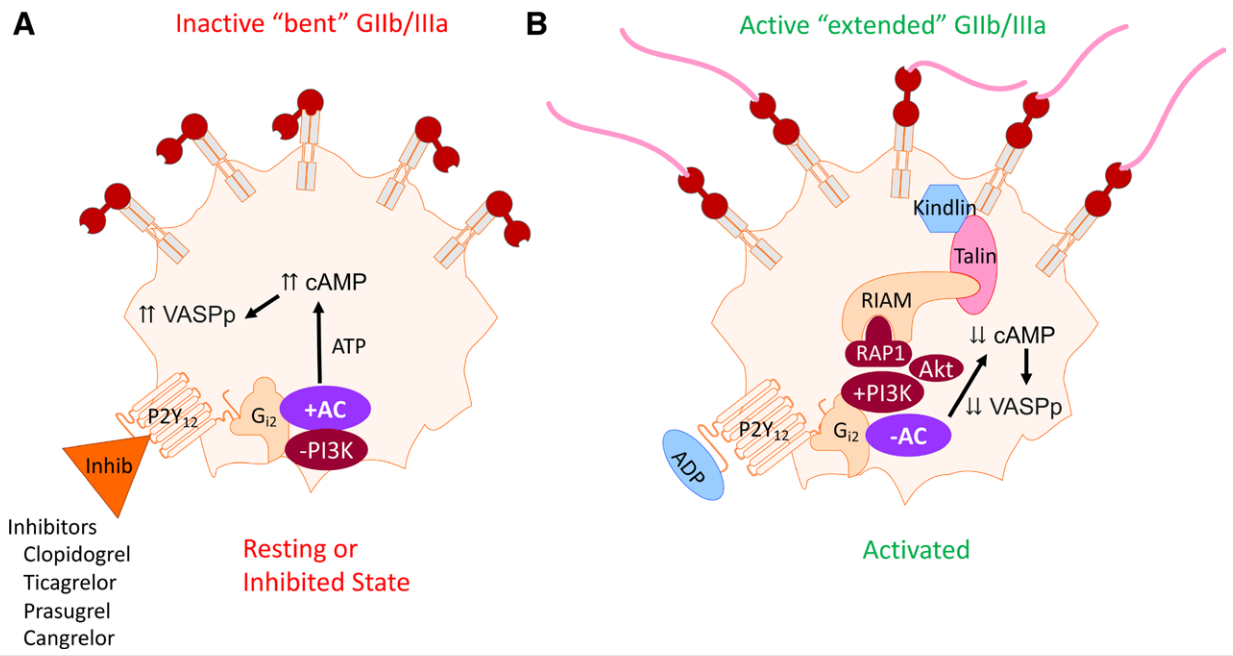

Fig. 1. The GPIIb/IIIa protein (Integrin $\alpha_{IIb}\beta_3$) is the most common platelet surface protein, with approximately 50,000 to 80,000 copies expressed on each platelet surface. GPIIb/IIIa is also stored in platelet α-granules, and expression can be increased by up to 50% during platelet activation. The α_{IIb} portion is composed of 1,008 amino acids, and the β_3 portion is composed of 762 amino acids. Both proteins have extracellular, transmembrane, and cytoplasmic domains. The two proteins form a heterodimer that is noncovalently bonded. GPIIb/IIIa has both adhesion and signaling functions. In its "nonactivated" conformation (*A*), GPIIb/IIIa is bent and closed. When activated (*B*), its structure changes to an extended open configuration, allowing for binding to fibrinogen, fibrin, fibronectin, and von Willebrand factor. Activation of GPIIb/IIIa occurs through intracellular "inside-out" signaling, in which Rap1, Rap1–guanosine triphosphate (GTP)–interacting adaptor molecule (RIAM), and talin are the final activating complex. The intracellular protein kindlin is an important coactivator of GPIIb/IIIa. P2Y$_{12}$ is a transmembrane G-protein–coupled receptor that effects both adenylate cyclase (AC) and phosphoinositide 3-kinase (PI3K) signaling inside platelets. Under resting or inhibitory conditions, P2Y$_{12}$ upregulates the activity of AC increasing cyclic adenosine monophosphate (cAMP) concentration and also increasing phosphorylated vasodilator-stimulated phosphoprotein (VASP). When adenosine diphosphate (ADP) interacts with the P2Y$_{12}$ receptor, cAMP concentration decreases, VASP decreases, and PI3K signaling increases, leading to activation of GPIIb/IIIa through the Rap1–RIAM–talin complex. AKT, protein kinase; AKTPI3K, phosphoinositide 3-kinase; Inhib, inhibitor; Kindlin, kindlin protein; Talin, talin protein,

could be used to inhibit or to reverse platelet aggregation in thrombosis."

P2Y$_{12}$ Receptor Inhibitor Drugs

There are currently four U.S. Food and Drug Administration (FDA; Silver Spring, Maryland)–approved P2Y$_{12}$ inhibitors available in the US (Table 1): clopidogrel, prasugrel, ticagrelor, and cangrelor. The four drugs differ in their potency, route of administration, half-life, and ability to be reversed with currently available therapies. A fifth drug, selatogrel, has received fast-track designation from the FDA and is currently in phase III clinical trials.

Thienopyridines

Clopidogrel and prasugrel are second-generation prodrugs with a common structure, a paired pyridine–thiophene ring. The first-generation thienopyridine drug approved by the FDA, ticlopidine, is no longer available in the United States, largely because of concerns about thrombotic thrombocytopenic purpura and associated neutropenia.[12–14]

Clopidogrel

Clopidogrel is an oral prodrug that became FDA-approved in 1997.[14] After oral administration, it is metabolized in a hepatic cytochrome P450-based two-step process.[14] First, it is oxidized into an inactive intermediate, and then, it is converted to an active thiol form *via* CYP2C19 (major cytochrome), CYP3A, CYP2B6, and CYP1A2 enzymes.[14] The short-lived thiol active metabolite binds to the P2Y$_{12}$ receptor *via* a disulfide bridge between the reactive thiol group and two cysteine residues (Cys-17 and Cys-270) present in the extracellular domains of the P2Y$_{12}$ receptor.[15] Thus, the binding of ADP to the P2Y$_{12}$ receptor is permanently inhibited for the life of the platelet.[15]

Early *ex vivo* experiments demonstrated clopidogrel's ability to synergistically inhibit platelet aggregation with aspirin, and together, the drug combination reduced

Table 1. FDA-approved $P2Y_{12}$ Receptor Inhibitors and Their Characteristics

Drug	FDA Approval and Indications	Mechanism	Route of Administration and Dose	Half-life	Metabolism/Elimination	Recommended Withholding before Elective Surgery	Unique Considerations
Clopidogrel	Approved in 1997 Acute coronary syndrome Prevention of cardiovascular events after recent MI, stroke, or in cases of established PVD	Thienopyridine Irreversible binding of active metabolite to $P2Y_{12}$ receptor on platelets, leads to inhibition of aggregation for life of platelet	Oral 300-mg dose for "loading" 75 mg/day maintenance dose	6 h for drug 30 min for active metabolite	Metabolism by esterases and P450 enzymes Prodrug with two-step metabolism to active metabolite Final conversion to active metabolite occurs through CYP2C19, CYP3A, CYP2B6, and CYP1A2 enzymes in the liver Peak drug effect observed 2–4 h after administration Eliminated in urine and feces (approximately equal)	5 days	Drug interaction with PPIs, leading to decreased active drug CYP2C19 genotype leads to variable metabolism CYP2C19*2 and *3 alleles account for majority of poor metabolizers
Prasugrel	Approved in 2009 Acute coronary syndrome	Thienopyridine Irreversible binding of active metabolite to $P2Y_{12}$ receptor on platelets, leads to inhibition of aggregation for life of platelet	Oral 60-mg dose for "loading" 10 mg/day maintenance dose	Prodrug rapidly metabolized 7 h for active metabolite	Prodrug with single step conversion to active drug by CYP3A4 and CYP2B6 50% inhibition of platelet aggregation occurs 1 h after administration Eliminated in urine (two thirds) and feces (one third)	7 days	Contraindicated in patients with a history of prior TIA or stroke Cases of TTP have been reported with use No significant CYP genotype effects observed
Ticagrelor	Approved in 2011 To reduce rate of cardiovascular death, MI, stroke in patients with recent ACS or history of MI	Nonthienopyridine inhibitor of $P2Y_{12}$, has reversible binding to $P2Y_{12}$, inhibiting platelet aggregation Both ticagrelor and its active metabolite inhibit $P2Y_{12}$ equally	Oral 180-mg dose for "loading" 90 mg/day maintenance dose during first year and then 60 mg twice per day		Active drug with active metabolite, no metabolism required for drug effect Metabolized by CYPA34 Peak drug effect observed 1–2 h after administration, rapid increase in platelet inhibition within 1 h Eliminated in urine (one third) and feces (two thirds)	5 days	Contraindicated in patients with a history of ICH Can lead to ventricular pauses and bradycardia, also dyspnea Strong inhibitors of CYP3A (*e.g.*, ketoconazole, clarithromycin) increase drug concentration and bleeding risk Strong inducers of CYP3A (*e.g.*, rifampin, phenytoin) reduce drug concentration and decrease drug efficacy Higher percentage of inhibition of platelet aggregation compared to clopidogrel
Cangrelor	Approved in 2015 Periprocedure adjunct for PCI	Nonthienopyridine inhibitor of $P2Y_{12}$, has reversible binding to $P2Y_{12}$, inhibiting platelet aggregation	Intravenous 30-μg · kg^{-1} bolus followed by 4-μg · kg^{-1} · min^{-1} infusion	3–6 min	Active drug, no metabolism required for drug effect Peak drug effect within 2 min of bolus Metabolism independent of hepatic function, related to dephosphorylation	25–30 min	When transitioning to ticagrelor, ticagrelor can be given during cangrelor infusion When transitioning to clopidogrel or prasugrel, the drugs must be given after discontinuation of cangrelor

ACS, acute coronary syndrome; FDA, Food and Drug Administration; ICH, intracranial hemorrhage; MI, myocardial infarction; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; PVD, peripheral vascular disease; TIA, transient ischemic attack; TTP, thrombotic thrombocytopenic purpura.

platelet thrombus mass by as much as 50 to 70% under high shear.[16,17] In multiple subsequent studies, clopidogrel also demonstrated significant interpatient variability regarding platelet inhibition.[18,19] In one study of 96 patients undergoing PCI, clopidogrel resistance was observed in 31% of patients 5 days after treatment.[18] In a second study, 41% of

patients were nonresponders based on light transmittance aggregometry.[20]

Subsequently, the same phenomenon has been observed worldwide in large numbers of patients undergoing PCI. Multiple lines of evidence now suggest that variable and insufficient active metabolite generation are the primary explanations for clopidogrel response variability and nonresponsiveness, respectively.[19,21] Variable levels of clopidogrel active metabolite may be due to single-nucleotide polymorphisms of specific genes encoding CYP450 isoenzymes, particularly CYP2C19 enzymes, as well as functional variability in P450 isoenzyme activity due to drug–drug interactions, coadministration of proton pump inhibitors, lipophilic statins, calcium channel blockers, and tobacco use.[21,22]

Although a diminished level of platelet inhibition induced by clopidogrel has been demonstrated in some *ex vivo* studies after the coadministration of the previously mentioned drugs, the clinical consequences of these interactions remain controversial.[23] Multiple translational research and registry studies have suggested an association between high platelet reactivity to ADP in the presence of clopidogrel and recurrent ischemic events, particularly in coronary artery disease patients treated with coronary artery stenting.[24,25]

Despite its limitations, clopidogrel remains the most widely prescribed $P2Y_{12}$ inhibitor in the United States, accounting for 80 to 90% of prescriptions.[26] Genetic testing to evaluate clopidogrel metabolization is available, including through home genetic tests. The published literature is mixed on whether genetic testing should be performed and is cost-effective in the modern era, especially when other $P2Y_{12}$ inhibitors are available, albeit with a higher bleeding risk.[27,28]

Prasugrel

Prasugrel is a prodrug fully absorbed from the gastrointestinal tract after oral administration and requires a single rapid conversion step to achieve its active thiol form.[29] Enzymatic conversion of prasugrel to its active metabolite occurs through CYP3A4 and CYP2B6 enzymes. Due to efficient active metabolite generation, prasugrel is a more potent and rapid inhibitor of platelet aggregation than clopidogrel.[30–32] Prasugrel is also less affected by other drugs that inhibit or induce the P450 system compared to clopidogrel.[33]

Prasugrel's efficacy in patients with acute coronary syndrome was established in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON-TIMI 38). In this study, prasugrel significantly decreased the incidence of recurrent myocardial infarction and the composite outcome of adverse cardiovascular events compared to clopidogrel, with an effect apparent within 30 days of treatment.[34] However, these benefits were associated with significantly increased key safety endpoints of thrombolysis in myocardial infarction (TIMI) major bleeding, including life-threatening and fatal bleeding in patients treated with prasugrel.[34]

The FDA has approved a maintenance dose of 5 mg in patients weighing less than 60 kg because of the potential for increased bleeding; however, the effectiveness and safety of the 5-mg dose have not been studied prospectively in a PCI trial. Prasugrel is not recommended in patients with active pathologic bleeding or a history of transient ischemic attack or stroke. In patients 75 yr of age or older, prasugrel is generally not recommended because of the increased risk of fatal or intracranial bleeding. Hence, the main drawbacks of prasugrel are its significant bleeding risk and the relatively long half-life of its active metabolite, which is approximately 7 h.[35–37]

Ticagrelor

Ticagrelor (AZD6140), a cyclopentyltriazolopyrimidine derivative, is an oral, reversibly binding, direct-acting $P2Y_{12}$ inhibitor. Ticagrelor is an active drug and does not require conversion by the cytochrome P450 system to inhibit platelet aggregation. Ticagrelor has an active metabolite (AR-C124910XX) that also inhibits platelet aggregation in an equipotent fashion. Ticagrelor is associated with a rapid onset of action, a greater level of platelet inhibition during maintenance therapy, and a more rapid offset of pharmacodynamic action compared with clopidogrel.[38]

Ticagrelor has been FDA-approved since 2011 for the treatment of acute coronary syndrome and to reduce adverse cardiovascular events in patients with a history of prior myocardial infarction. Several studies established ticagrelor's efficacy and superiority over clopidogrel for the first 12 months after acute coronary syndrome. In the Ticagrelor *versus* Clopidogrel in Patients with Acute Coronary Syndromes (PLATO) trial, patients who were treated with ticagrelor had a 1.9% absolute risk reduction for adverse cardiovascular events during the first 12 months after treatment.[39] Any cause mortality was also 1.4% lower in patients treated with ticagrelor.[39] Ticagrelor has pleiotropic effects that may explain why it reduces myocardial injury after ischemia or reperfusion, improves coronary blood flow, and is associated with reduced inflammation compared to other $P2Y_{12}$ inhibitors.[40,41] It has a bioavailability of 35% after ingestion, with significant platelet inhibition achieved by 30 min and peak drug effect achieved by 2 h.[42,43]

Ticagrelor therapy is associated with several side effects, including dyspnea (which occurs in at most 15% of patients within the first week of treatment but is rarely severe enough to cause discontinuation of treatment) and bradycardia. The exact cause of these side effects is not clear but may be related to inhibition of adenosine reuptake. Current guidelines recommend using a 180-mg ticagrelor loading dose followed by 90 mg twice daily with 81 mg of aspirin daily as part of dual antiplatelet therapy for 12 months in all patients with non–ST-elevation–acute coronary syndrome and also favor ticagrelor over

clopidogrel in general.[44,45] Ticagrelor is contraindicated in patients with a history of intracranial hemorrhage and is associated with bradyarrhythmias, including second- and third-degree heart block. CYP3A4 metabolizes ticagrelor and is subject to significant drug interactions. Inhibitors of CYP3A4 (*e.g.*, ketoconazole, voriconazole, ritonavir) increase ticagrelor concentration, whereas inducers (*e.g.*, rifampin, phenytoin) decrease its concentration. In the Long Term Use of Ticagrelor in Patients with Prior Myocardial Infarction (PEGASUS) TIMI-54 trial, patients with a history of myocardial infarction were randomized to receive aspirin alone or aspirin with ticagrelor.[46] Patients who received aspirin with ticagrelor had a lower incidence of adverse cardiovascular events, sustained for up to 4 yr after surgery.[46] Because both prasugrel and ticagrelor are associated with more potent platelet inhibition compared to clopidogrel, they are a credible choice in patients with high platelet reactivity during clopidogrel therapy or in patients with genetic polymorphisms of CYP2C19.[20,47]

Cangrelor

Cangrelor was FDA-approved in 2015 and is currently the only intravenous $P2Y_{12}$ receptor inhibitor. It is an active drug with a short half-life of 2 to 5 min and inhibits platelet aggregation by 60% at 5 min, with peak inhibition occurring at approximately 30 min to 1 h after starting treatment.[48]

Cangrelor is FDA-approved as an adjunct during PCI to reduce the risk of periprocedure myocardial infarction and stent thrombosis. Cangrelor is also used off-label in critically ill hospitalized patients who require dual antiplatelet therapy but are at high bleeding risk or are likely to require surgical intervention, where dual antiplatelet therapy must be held.

Cangrelor was studied in the Effect of Platelet Inhibition with Cangrelor during PCI on Ischemic Events (CHAMPION PHOENIX) trial as an adjunct in patients undergoing PCI.[49] In this trial, periprocedural dual antiplatelet therapy with aspirin and cangrelor was compared against aspirin and clopidogrel. Patients who were treated with aspirin and cangrelor had a significantly lower (1.2%) incidence of adverse cardiovascular events, which was mainly due to fewer periprocedural myocardial infarctions based on biomarker measurement.[49] Two subsequent trials of cangrelor in similar patients were terminated due to a lack of apparent benefit.[50,51]

Selatogrel

In high-thrombotic-risk patients who require urgent surgery, a novel $P2Y_{12}$ receptor inhibitor, selatogrel, may be an optimal choice. It is a subcutaneously administered 2-phenylpyrimidine-4-carboxamide analog with reversible $P2Y_{12}$ receptor biding properties and a half-life of 2 to 3 h.[52] In a recent study of patients with chronic coronary artery disease, a single 8- or 16-mg dose of selatogrel was associated with rapid and potent peak inhibition of platelet aggregation by 30 min. The drug's effect was sustained for up to 8 h, and by 24 h patients' platelet aggregation returned to baseline values due to drug metabolism and elimination.[52] Selatogrel is not currently FDA-approved for use in the United States and is associated with dyspnea similar to ticagrelor.[52]

Excess Bleeding in Surgical Patients Treated with $P2Y_{12}$ Inhibitors

Comparative Bleeding Risk between Long-acting Drugs

Due to their more potent platelet inhibition, prasugrel and ticagrelor are associated with a higher bleeding risk than clopidogrel. In a cohort study of almost 12,000 patients who underwent PCI, ticagrelor use was associated with 50% higher odds of major bleeding over time compared to clopidogrel.[53] In the PLATO trial, ticagrelor was associated with a higher risk of major bleeding after coronary artery bypass grafting (CABG; 4.5% *vs.* 3.8%) compared to clopidogrel, although the incidence of major bleeding among all patients (surgical and nonsurgical) was similar between groups.[39] In a recent systematic review and meta-analysis with nearly 30,000 patients, prasugrel therapy was associated with a 20% increase in major bleeding compared to clopidogrel.[35] Similar findings were reported in a network meta-analysis of greater than 52,000 patients in which treatment with ticagrelor or prasugrel was associated with a 25% increased risk of major bleeding compared to clopidogrel.[54]

Cardiac Surgical Patients

The majority of studies that have reported elevated bleeding risk in cardiac surgical patients receiving $P2Y_{12}$ inhibitors are in CABG patients. In one study of 453 off-pump CABG patients, 100 of whom were taking aspirin and clopidogrel before surgery, patients taking dual antiplatelet therapy had higher intraoperative (702 ml *vs.* 554 ml; $P = 0.03$) and postoperative blood loss (865 ml *vs.* 604 ml; $P = 0.03$) compared to aspirin alone.[55] Among the 100 patients taking dual antiplatelet therapy, 37% received a dose of clopidogrel within 72 h of surgery. Overall, dual antiplatelet therapy patients received more erythrocyte and platelet transfusion, but there was no association with reoperation for bleeding.[55] The association between dual antiplatelet therapy and excess bleeding was attenuated when dual antiplatelet therapy was stopped more than 72 h before surgery, suggesting that withholding clopidogrel for 72 h before CABG may be adequate in some cases.[55]

In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, patients who stopped taking clopidogrel 5 or more days before surgery had no excess risk for major bleeding during the first 7 days after

surgery (4.4% *vs.* 5.3%) compared to patients taking aspirin alone.[56] In patients who received clopidogrel within 5 days of surgery, there was a trend toward more major bleeding (9.6% *vs.* 6.3%; $P = 0.06$), and there was also more minor bleeding (5.1% *vs.* 2.4%; $P < 0.001$).[56] In a study of 1,173 patients having on-pump CABG, clopidogrel use within 7 days of surgery (mean duration of withholding 5 days) was associated with excess blood loss, increased erythrocyte transfusion volume, and a higher percentage of patients receiving erythrocyte transfusion.[57] There was, however, no increase in reoperation for bleeding with clopidogrel use, and tranexamic acid treatment significantly reduced excess bleeding related to clopidogrel.[57]

There are no randomized placebo-controlled trials in CABG patients treated with prasugrel to analyze bleeding risk. In the TRITON-TIMI 38 trial, CABG patients treated with prasugrel had a 13.4% rate of major bleeding after surgery, which was four-fold higher than in patients treated with clopidogrel.[34] In a *post hoc* analysis, total blood loss in the first 12 h after surgery was 655 ml for CABG patients treated with prasugrel, 153 ml higher than in the clopidogrel group.[58] In a cohort study of 299 patients undergoing CABG in which 83% of patients received dual antiplatelet therapy within 48 h of surgery, calculated total blood loss was 1,351 ml for patients taking prasugrel, which was 288 ml higher than in patients taking clopidogrel.[59] Bleeding Academic Research Consortium (BARC) class 4 bleeding was also higher in patients who received prasugrel.[59]

There are also no randomized placebo-controlled trials to elucidate excess bleeding risk with ticagrelor in CABG patients. Most data are derived from comparative studies against clopidogrel and prasugrel. In the previously mentioned Voetsch trial of 299 CABG patients, those who were taking ticagrelor had nearly identical estimated blood loss compared to those who received prasugrel (1,330 ml *vs.* 1,351 ml), which was significantly higher than in patients who received clopidogrel.[59] In a Swedish cohort study that compared patients treated with ticagrelor *versus* clopidogrel before CABG, the authors found that 24-h blood loss was similar when comparing all patients; however, there were fewer major bleeding complications in patients treated with ticagrelor.[60] In this study, 44% of patients took clopidogrel within 5 days of surgery, and 33% took ticagrelor within 3 days. For patients taking ticagrelor, excess bleeding risk appeared to be mitigated with 3 days of withholding, whereas for clopidogrel, 5 days of withholding mitigated bleeding risk.[60] Similar results were reported in an observational study of CABG patients in which patients who stopped ticagrelor within 2 days of CABG had a major bleeding rate of 16% compared to a major bleeding rate of 2.7% in those who stopped ticagrelor 3 or more days before surgery.[61]

Synthesizing the available data from CABG patients, bleeding risk is related to the timing of last drug administration and the specific $P2Y_{12}$ receptor inhibitor that was taken. For most patients taking clopidogrel, it appears that bleeding risk declines significantly after 3 to 5 days of drug withholding. For patients taking ticagrelor and prasugrel, bleeding risk declines significantly after 3 and 7 days of drug withholding, respectively.

Noncardiac Surgical Patients

Bleeding data for noncardiac surgical patients taking $P2Y_{12}$ inhibitors are more limited. In a small cohort study of 29 patients, including both cardiac and noncardiac surgical patients (four neurosurgical patients, three orthopedic patients, two thoracic patients, and three other noncardiac surgical patients), most patients were on aspirin and clopidogrel before surgery.[62] In this study, the average discontinuation time before surgery was 2.8 days, and all patients had platelet aggregation evaluated using multiple impedance aggregometry before surgery. The authors found that the relationship between multiple impedance aggregometry values and last $P2Y_{12}$ inhibitor treatment time was extremely variable.[62] Two patients experienced major bleeding complications (both neurosurgical patients), despite having multiple impedance aggregometry area under the curve values in the 40- to 50-unit range (local reference range in healthy adults, 36 to 93 units) before surgery, which were two of the higher values in the cohort.[62] These data suggest that patients who are taking $P2Y_{12}$ inhibitors and require intracranial surgery may be at high risk for bleeding complications.

In another small cohort study of patients undergoing orthopedic surgical procedures (*e.g.*, spine instrumentation or hip arthroplasty), 16 patients received dual antiplatelet therapy with aspirin and clopidogrel throughout the perioperative period.[63] In this study, there was no difference in intraoperative or postoperative blood loss between patients who had dual antiplatelet therapy continued *versus* those who had clopidogrel held with continuation of aspirin.[63]

In a cohort study of 50 consecutive patients who were taking clopidogrel and had general surgical procedures performed, those who received clopidogrel within 6 days of surgery had a two-fold higher risk for bleeding complications (21.4% *vs.* 9.5%) compared to those who stopped clopidogrel for 7 or more days.[64] Similar results were found in a cohort study of 104 patients taking clopidogrel before major abdominal surgery in which there was an increased risk of postoperative bleeding when clopidogrel was taken within 6 days of surgery.[65] Vascular surgical patients who received clopidogrel within 36 h of their lower extremity bypass surgery had a higher risk for allogeneic transfusion and major blood loss exceeding 500 ml.[66] A systematic review and meta-analysis that included 12 studies of greater than 14,000 noncardiac surgery patients concluded that the preoperative use of clopidogrel increased the risk for major bleeding two-fold in noncardiac surgical patients.[67]

Monitoring of $P2Y_{12}$ Receptor Inhibitor Therapy

Platelet function testing in cardiac surgical patients taking antiplatelet drugs has previously been reviewed in detail in Anesthesiology by Mahla *et al.*[68] Nevertheless, several devices that can be used for monitoring of $P2Y_{12}$ inhibition are briefly discussed.

VerifyNow

The VerifyNow $P2Y_{12}$ reaction units test (Werfen, USA) has been FDA-approved since 2003 and is widely used to monitor antiplatelet effects of $P2Y_{12}$ inhibitors. It is a whole blood citrated turbidometric-based assay in which a change in light transmission is assessed in blood samples in the presence of fibrinogen-coated beads after stimulation with ADP/prostaglandin E1. The results are shown as $P2Y_{12}$ reaction units. The normal average reference range for $P2Y_{12}$ reaction units, established in healthy volunteers in the absence of antiplatelet agents is 194 to 418 $P2Y_{12}$ reaction units. Per the device's manufacturer, values less than 194 $P2Y_{12}$ reaction units highly suggest a significant $P2Y_{12}$ receptor inhibitor effect.

In patients taking clopidogrel who underwent urgent CABG, a $P2Y_{12}$ reaction units value of less than 204 $P2Y_{12}$ reaction units was associated with major bleeding.[69] A second study of 39 patients taking clopidogrel before CABG surgery found a similar cutoff value to predict major bleeding of 207 $P2Y_{12}$ reaction units.[70] In this study, for every 10-$P2Y_{12}$ reaction unit increase, the risk of major bleeding after CABG decreased by 14%.[70]

Although VerifyNow testing has been used as a preoperative test in cardiac surgery patients, platelet counts decrease in bleeding surgical patients, especially during cardiopulmonary bypass (CPB) due to dilution and consumption, and current data do not support its intraoperative use. The $P2Y_{12}$ reaction units test is highly influenced by hematocrit, which confounds its interpretation in cardiac surgical patients.[71] Hence, it is not used to monitor platelet function during or after CPB. Additional research is underway to develop platelet function testing in this setting.

Thromboelastography Platelet Mapping

The thromboelastography (TEG) platelet mapping assay is available on the TEG 6s *via* the platelet mapping cartridge. TEG platelet mapping uses kaolin to measure thrombin-induced maximum clot amplitude ($MA_{Thrombin}$). It also measures fibrin clot amplitude (MA_{Fibrin}) in the presence of activator F (reptilase and factor XIII) and a GPIIb/IIIa inhibitor, and ADP-stimulated clot amplitude (MA_{ADP}) in the presence of 10 μM ADP and activator F.[72] The percentage of $P2Y_{12}$ inhibition is then calculated using the following series of formulas:

$$\%\ \text{ADP stimulated aggregation} = [(MA_{ADP} - MA_{Fibrin})/(MA_{Thrombin} - MA_{Fibrin}) \times 100] \quad (1)$$

$$\%\ P2Y_{12}\ \text{inhibition} = (100\% - \%\ \text{ADP stimulated aggregation}) \quad (2)$$

TEG platelet mapping has been studied in patients taking clopidogrel before CABG. Among 182 patients who took clopidogrel within 7 days of surgery, those who had 30% or more $P2Y_{12}$ inhibition received significantly more erythrocyte transfusion.[73] In a second study that included only off-pump CABG patients (N = 100) who took clopidogrel within 5 days of surgery, 70% or more $P2Y_{12}$ inhibition was associated with significantly more transfusion, even after controlling for other confounders.[74] Finally, in a study of 434 patients taking dual antiplatelet therapy with aspirin and clopidogrel or aspirin and ticagrelor, 66% or more $P2Y_{12}$ inhibition was associated with a three-fold increased odds of BARC class 4 bleeding.[75] Synthesizing limited available data, it seems that 60 to 70% or more $P2Y_{12}$ inhibition on TEG platelet mapping is associated with major bleeding in cardiac surgical patients, and inhibition as low as 30%, may increase transfusion risk slightly. A significant limitation of using platelet mapping is its long turnaround time of approximately 45 min.[72]

Other $P2Y_{12}$ Tests

Additional commercially available devices and assays that can measure $P2Y_{12}$ inhibition but have limited published data to support specific cutoffs associated with surgical bleeding include the Multiplate analyzer with ADP test (Roche Diagnostics, Switzerland), rotational thromboelastometry (ROTEM) ADP-TEM (Werfen, Spain), the total thrombus analysis system (T-TAS) PL (platelet) chip (Zacros, Japan), and the Platelet Function Analyzer 200 collagen-ADP and P2Y tests (Siemens, Germany).[76–78] Both the total thrombus analysis system and Platelet Function Analyzer 200 evaluate platelet adhesion and subsequent aggregation under high shear conditions, which is unique compared to the low shear conditions that occur with traditional platelet aggregometry. In one recent study that evaluated the Platelet Function Analyzer 200 in cardiac surgical patients, a closure time greater than 106 s on the Platelet Function Analyzer 200 P2Y test was independently associated with the need for blood transfusion.[79]

Mitigating Perioperative Bleeding Risk

Strategies to mitigate perioperative bleeding risk in patients taking $P2Y_{12}$ receptor inhibitors can broadly be classified into (1) appropriate withholding of $P2Y_{12}$ inhibitors for elective surgery, (2) watchful waiting based on platelet function testing in cases of urgent surgery, and (3) preoperative and/or intraoperative platelet transfusion and use of other reversal strategies in cases of emergency surgery (fig. 2).

Drug Withholding and Watchful Waiting Based on Platelet Function Testing

Table 1 lists recommended withholding intervals for $P2Y_{12}$ receptor inhibitors in elective surgery cases: 5 days for ticagrelor, 5 days for clopidogrel, 7 days for prasugrel, and

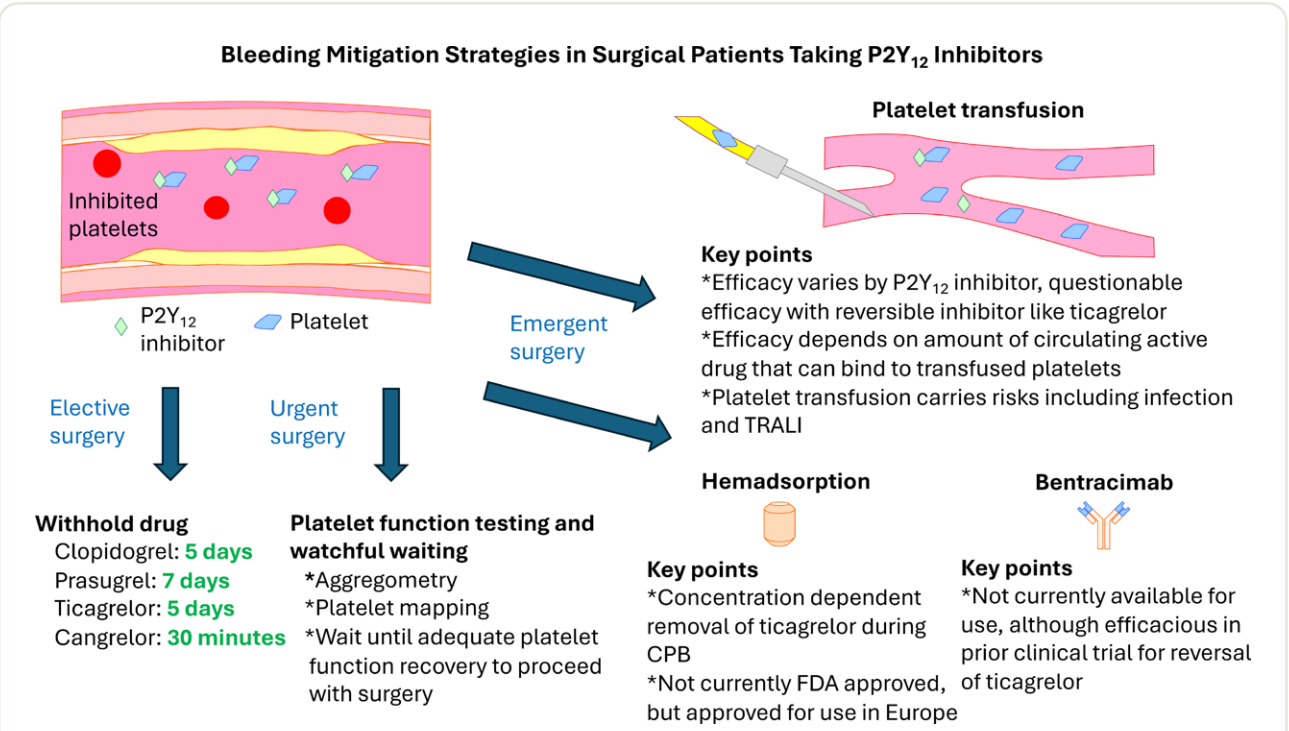

Fig. 2. The figure summarizes bleeding mitigation strategies in surgical patients taking $P2Y_{12}$ inhibitors who present for elective, urgent, and emergent surgery. CPB, cardiopulmonary bypass; FDA, Food and Drug Administration; TRALI, transfusion related acute lung injury.

30 min for cangrelor. The use of platelet function testing to guide surgery timing in patients taking $P2Y_{12}$ inhibitors who require urgent surgery has been previously described in detail in Anesthesiology.[68] VerifyNow or TEG 6s platelet mapping can be used to monitor drug washout and return of acceptable platelet aggregation. If VerifyNow is used, PRU should be greater than 200 PRU to limit the risk of major bleeding.[69,70] If TEG platelet mapping is used, platelet inhibition should be less than 70%[73] or MA_{ADP} greater than 50 mm.[80]

Platelet Transfusion for Acute Drug Reversal

Allogeneic platelet transfusion is the most common treatment used to acutely reverse the effects of $P2Y_{12}$ inhibitors in surgical patients. Notably, there is weak evidence to support its efficacy, with no evidence from randomized controlled trials. Also, platelet transfusion efficacy probably depends on the timing of the last drug administration, the specific $P2Y_{12}$ inhibitor, and possibly platelet storage duration. Room temperature–stored allogeneic platelets demonstrate weak *in vitro* responses to ADP stimulation, with a rapid decline greater than 7 days.[81,82] Recent studies suggest that with cold storage at 4°C, there may be better preservation of ADP-induced platelet aggregation, but more studies are needed to confirm this finding.[83]

In a small study of 10 patients, Cohn *et al.*[84] collected an apheresis unit of platelets from patients and stored them either warmly or coldly at two separate time points.[84] Patients were treated with aspirin and clopidogrel (325 and 75 mg, respectively) for 3 days and then had their platelets (both stored warmly and coldly) retransfused.[84] Bleeding time was prolonged significantly after treatment (around three-fold), and platelet transfusion (neither warm nor cold stored) did not improve bleeding time back to its baseline value.[84] The authors concluded that platelet transfusion did not reverse excess clinical bleeding related to aspirin and clopidogrel effect.

In an *in vitro* study, Teng *et al.*[85] studied blood from 44 healthy volunteers who ingested either a clopidogrel or ticagrelor loading dose and aspirin. Patients were transfused a single apheresis platelet unit 24 h after ticagrelor or 48 h after clopidogrel. The authors found that in patients who had received ticagrelor, there was no improvement in platelet aggregation measured by light transmission aggregometry at any point after platelet transfusion for up to 3 days.[85] In contrast, in patients treated with clopidogrel, there were slight increases in platelet aggregation observed 24, 36, and 48 h after platelet transfusion.[85] VerifyNow $P2Y_{12}$ reaction units values were slightly higher in ticagrelor-treated patients who were transfused 72 h after transfusion.[85] PRU values were also higher in clopidogrel-treated patients transfused with platelets 12, 24, and 36 h after transfusion.[85] The authors concluded that allogeneic platelet transfusion is more likely to be effective for clopidogrel reversal compared to ticagrelor.

In another study, the authors explored the impact of adding either plasma or gel-filtered platelets from patients who were treated with clopidogrel (75 mg per day), prasugrel (10 mg per day), or ticagrelor (90 mg twice per day) to donor platelet-rich plasma. The authors found that platelet responsiveness to ADP was "dramatically reduced" by adding even diluted plasma or gel-filtered platelets from ticagrelor-treated patients.[86] In contrast, the addition of plasma or gel-filtered platelets from patients taking clopidogrel or prasugrel had minimal effect. The authors concluded that ticagrelor present in plasma or bound to the $P2Y_{12}$ receptor on platelet surfaces inhibits the function of transfused platelets.[86] In a similar *in vitro* study, Zhang *et al.*[87] found that when blood samples from patients taking ticagrelor had normal platelets added *in vitro*, ADP-induced platelet aggregation did not improve, even when up to 90% of platelets present in the sample were normal control platelets.

In contrast, a study from Zafar *et al.*[88] found that *in vitro* platelet supplementation could improve platelet aggregation in blood samples from patients taking ticagrelor. The authors added normal platelets to increase platelet count by 25, 50, and 75%.[88] At 24 h after ticagrelor treatment, they observed improvements in platelet aggregation back to near 60 to 80% of baseline values, and by 48 h after treatment, they were able to normalize platelet aggregation with *in vitro* platelet supplementation.[88] Notably, this study used fresh, healthy donor platelets, not platelets that had been stored for several days, and hence, it may not be reflective of actual clinical conditions.

In a clinical study of 14 patients receiving dual antiplatelet therapy with aspirin and clopidogrel requiring urgent surgery, the authors waited 12 to 24 h to allow for clearance of aspirin and clopidogrel's active metabolites.[87] They then transfused two platelet units 1 to 2 h before surgery.[89] With this strategy, only one patient (7.1%) had a significant bleeding complication after surgery, and one patient had acute coronary syndrome.[89] Anders *et al.*[90] reported a 9.9% incidence of bleeding complications in cardiac surgical patients who were transfused platelets to reverse the antiplatelet drug effect and a 26% incidence in noncardiac surgical patients. The authors did not report the timing of last antiplatelet drug administration.

Synthesizing the available data, it seems plausible that platelet transfusion improves platelet aggregation in patients taking clopidogrel and possibly prasugrel, particularly if the last drug administration was longer than 24 h before and if active metabolites have cleared.[91] Both clopidogrel and prasugrel bind irreversibly to $P2Y_{12}$ and do not diffuse off bound platelet $P2Y_{12}$ receptors to inhibit transfused platelets. In patients taking ticagrelor, *in vitro*, the data are mixed, but the majority of studies suggest that platelet transfusion is probably of limited efficacy because ticagrelor and its active metabolites are reversibly bound to $P2Y_{12}$ receptors and are redistributed to $P2Y_{12}$ receptors on platelets in the transfused unit.

Platelet transfusion is associated with significant risks, which should also be considered when treating $P2Y_{12}$ receptor inhibitor drug-related bleeding. A recent report from the National Healthcare Safety Network hemovigilance module reported that 1 in 200 patients who received an apheresis platelet transfusion experienced an adverse reaction.[92] Adverse reactions are highest when platelets are suspended in plasma compared to platelet additive solution and are most commonly allergic.[92] Platelet transfusion has historically been associated with risks of bacterial contamination, sepsis, and transfusion-related acute lung injury.[93,94] Bacterial contamination and sepsis risks have likely been reduced by pathogen reduction, but large epidemiologic studies are needed to confirm its efficacy.[95] Also, there remain questions about how pathogen reduction affects the hemostatic efficacy of transfused platelets.[95] Platelet transfusion is also associated with increased mortality in some specific groups of patients who experience bleeding while taking $P2Y_{12}$ inhibitors, including those with gastrointestinal bleeding.[96]

Hemadsorption for Acute Reversal of Ticagrelor

Copolymer adsorbents made from styrene, including Porapak Q 50-90 mesh and CytoSorb, have large surface areas of 550 and 850 m^2/g, respectively, which allow for efficient hemadsorption of various biologically active molecules, including ticagrelor.[97] Adsorption occurs *via* van der Waals forces, which are weaker than covalent or ionic bonds but are sufficient for drug removal. Hemadsorption filters are typically inserted into the CPB circuit using a side-arm connection in which blood flows into the filter from the positive pressure side of the CPB circuit (postpump and preoxygenator) and is returned into the venous reservoir.

Ticagrelor is effectively removed from blood *in vitro* using both CytoSorb (CytoSorbents Corp., USA) and Porapak Q 50 to 90 mesh (Sigma-Aldrich, USA) with up to 99 to 100% of ticagrelor removed, and the vast majority in the first 3 to 4 h.[97] Ticagrelor is highly bound to albumin *in vivo* but can be removed efficiently, even if the concentration of albumin varies. Notably, adsorption removes albumin, albeit to a lesser degree (less than 10%). Removal of ticagrelor by hemadsorption is both concentration and time-dependent, and hence, in short CPB cases or cases of lower baseline ticagrelor concentration, removal may be incomplete.

In a cohort study of patients with acute type A aortic dissection, there were 12 patients taking ticagrelor immediately before surgery.[98] All patients were treated with CytoSorb in the CPB circuit, and bleeding and transfusion were compared against historical controls.[98] Patients treated with CytoSorb had approximately half the chest drain output and received fewer platelet transfusions.[98] There were also no reoperations for bleeding compared with a 19% reoperation rate in historical controls.[98]

In a second study in which 43 patients who received ticagrelor before cardiac surgery had hemadsorption performed

during CPB, Hassan *et al.*[99] found low postoperative chest drain output (median, 350 ml), as well as low transfusion and reoperation rates when compared to a historical group of controls who did not receive hemadsorption. Currently, CytoSorb is approved use in the European Union for ticagrelor removal during CPB, but it is not approved in North America. At the time of this article's writing, the Safe and Timely Antithrombotic Removal–Ticagrelor (STAR-T) randomized, controlled trial has completed enrollment and should provide additional data on CytoSorb's efficacy for ticagrelor removal during CPB.[100]

Initial, unpublished results from STAR-T were presented at the American Association of Thoracic Surgery annual meeting in Toronto in 2024.[101] Patients who received treatment with hemadsorption in the full study cohort did not have a significant benefit in terms of the study's primary outcome, which was a composite of fatal perioperative bleeding; moderate, severe, or massive bleeding according to the Universal Definition of Perioperative Bleeding in Cardiac Surgery; and 24-h chest tube drainage. However, isolated CABG patients, who were analyzed as a predefined subgroup, had a lower incidence of severe bleeding, suggesting that at least some patients are likely to benefit from treatment with hemadsoprtion.

Bentracimab for Acute Reversal of Ticagrelor

Bentracimab (PB2452; PhaseBio, USA) is a recombinant monoclonal antibody fragment developed to bind ticagrelor and its active metabolite.[102] In healthy volunteers, a bentracimab bolus and subsequent infusion led to near complete ticagrelor reversal with a sustained effect and excellent safety profile.[102] In a study of 150 patients who had taken ticagrelor within 3 days of surgery (142 surgical patients), bentracimab administration was associated with reversal of ticagrelor's antiplatelet effects within 5 to 10 min.[103] $P2Y_{12}$ reaction units values increased from a mean value of 65 $P2Y_{12}$ reaction units to 230 $P2Y_{12}$ reaction units within 5 to 10 min of administration of bentracimab and remained between 230 and 300 $P2Y_{12}$ reaction units for 24 h.[103] Approximately 72 h after infusion, $P2Y_{12}$ reaction units values declined modestly to approximately 200 $P2Y_{12}$ reaction units.[103] Although it has demonstrated efficacy in clinical trials, bentracimab is not currently available in the United States.

Desmopressin for Acute Drug Reversal

Desmopressin, which interacts with V2R receptors on endothelial cells, causing release of large von Willebrand factor multimers, has been evaluated as an adjunctive therapy for patients taking $P2Y_{12}$ inhibitors who experience major bleeding. In a study of 209 patients with intracranial hemorrhage (around 25% of whom were on dual antiplatelet therapy), 118 of whom received desmopressin, no significant reduction in hematoma expansion was observed with desmopressin treatment.[104] Similarly, desmopressin did not significantly reduce bleeding time in healthy volunteers taking ticagrelor.[105] Based on extremely limited published data, desmopressin cannot be recommended as a routine adjunctive treatment for patients taking $P2Y_{12}$ inhibitors with major bleeding.

Thrombotic Risk Associated with Acute Reversal

Patients treated with coronary artery stents in whom $P2Y_{12}$ inhibitors were held and received procoagulant treatments such as platelet transfusion may be at risk for recurrent acute coronary syndrome. The risk is highest if antiplatelet agents are withheld shortly after coronary artery stent placement but appears to decrease significantly after 12 months in patients with drug-eluting stents. In studies where $P2Y_{12}$ inhibitors were held, and platelet transfusion was administered, the incidence of acute coronary syndrome appears to be between 5 and 7%, but most cases are not due to stent thrombosis.[88,106] Early stent thrombosis is preventable in most patients by continuing aspirin throughout the perioperative period.[107]

Summary

$P2Y_{12}$ inhibitors continue to be a mainstay of dual antiplatelet therapy after PCI and have additional indications in peripheral vascular disease, cerebrovascular disease, and stable ischemic heart disease. In cases of elective surgery, appropriate withholding recommendations should be followed. Hemadsorption can be used in the CPB circuit for patients who require emergent cardiac surgery in Europe. In North America, platelet transfusion remains the only currently available treatment for reversal of $P2Y_{12}$ inhibitors in cardiac surgical patients and noncardiac surgical patients, but its efficacy remains unclear, particularly when transfused platelets have a long storage duration. Platelet transfusion appears to have some efficacy for patients taking clopidogrel and prasugrel, particularly if the drug and its active metabolites have cleared. In patients taking ticagrelor, platelet transfusion probably has limited efficacy. If urgent surgery is required, a 24- to 48-h delay is helpful because it allows the drug (*e.g.*, prasugrel or clopidogrel) and active metabolites to clear and improves the likelihood that platelet transfusion will be efficacious. When allowable, preoperative surgery timing can also be guided using assays such as VerifyNow (delay until PRU is greater than 200) or TEG platelet mapping (delay until there is less than 70% platelet inhibition), which will help to mitigate the risk of major bleeding.[69,70,75]

Acknowledgments

Motifolio, (Ellicott City, Maryland) was used to make the figures in this article.

Research Support

Support was provided solely from institutional and/or departmental sources.

Competing Interests

Dr. Mazzeffi received consulting fees from Hemosonics (Durham, North Carolina), Octapharma (Paramus, New Jersey), and NovoNordisk (Plainsboro, New Jersey). Dr. Tanaka has served on the advisory board for Werfen (Barcelona, Spain) and has received research funding from Cellphire (Rockville, Maryland), Octapharma, and Grifols (Barcelona, Spain). Dr. Gurbel received consulting fees and/or honoraria from Bayer (Whippany, New Jersey), Vectura/Otitopic (Los Angeles, California), Janssen (Beerse, Belgium), Cleveland Clinic Foundation (Cleveland, Ohio), Wolters Kluwer Pharma (Alphen aan den Rijn, Netherlands), Web MD Medscape (Newark, New Jersey), Baron and Budd (Dallas, Texas), Premier Health Care Resource (Jeannette, Pennsylvania), Baim Institute (Boston, Massachusetts), and Medforce (Shrewsbury, New Jersey); he received institutional research grants from Accriva Diagnostics (San Diego, California), AstraZeneca (Gaithersburg, Maryland), Bayer, Cronos (Toronto, Canada), Janssen Pharmaceuticals Inc. (Beerse, Belgium), Haemonetics (Boston, Massachusetts), Hikari Dx (San Diego, California), Idorisa (Basel, Switzerland), Labcorp Drug Development (Princeton, New Jersey), Novartis (Basel, Switzerland), Prolocor (Philadelphia, Pennsylvania), Recor Medical (Palo Alto, California), Vectura Limited (Chippenham, United Kingdom), and Zoll Medical Corporation (Chelmsford, Massachusetts); he has two patents: detection of restenosis risk in patients issued and assessment of cardiac health and thrombotic risk in a patient; and he was an expert witness in a lawsuit associated with Plavix. Dr. Tantry has received honoraria from Wolters Kluwer Pharma. Dr. Levy has served on steering committees for Merck (Rahway, New Jersey), Octapharma, Takeda (Tokyo, Japan), and Werfen.

Correspondence

Address correspondence to Dr. Mazzeffi: Department of Anesthesiology, University of Virginia Health, P.O. Box 800710, Charlottesville, Virginia 22908. mmazzeff@uvahealth.org

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