
New anticoagulants and antiplatelet agents

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HEMOSTASIS in cardiovascular patients is a challenge that clinicians have only begun to embrace. Caring for patients with cardiovascular disease requires an understanding of the etiology of the disease and the predisposing characteristics that make these patients hypercoagulable, hyperthrombotic, both, or neither. Patients host a heterogeneous complement of genetic and environmental factors which render them susceptible to arterial injury, atherosclerosis, inflammatory processes, thrombosis, and fibrinolysis.

Coupled with the complex pathophysiology of the vascular patient, are the unique hemostatic perturbations that occur as a result of cardiac surgery utilizing cardiopulmonary bypass (CPB). The presence of extracorporeal circuitry and the oxygenator have demanded meticulous attention to maintaining adequate anticoagulation during CPB. As we understand more about the limitations of heparin, and as new drugs become available for use, the search for new anticoagulants and alternative monitoring techniques during CPB will continue to progress.

Hemostasis after CPB is still a vexing problem. Patients having been exposed to antiplatelet medications in the preoperative period are particularly prone to bleeding after CPB. This is due to the additive effects of the antiplatelet therapeutics and the well-known platelet defects that occur as a result of CPB. The two opposing processes of anticoagulation and hemostasis must be managed carefully and modified with respect to the patient's hematologic status and desired hemostatic outcome. This review will summarize some potential new drugs for use as anticoagulants for cardiovascular procedures. Additionally, the new antiplatelet medications, and their respective mechanisms of activity will be described.

Anticoagulants

Heparin has been the gold standard for anticoagulation during cardiac surgery. Heparin has been used in a number of different dosing protocols and has proven

to be a relatively safe drug for this purpose.¹ Advantages of heparin include its rapid onset of activity, linear dose-response pharmacokinetics in the clinical range of use, and its ease of reversibility with protamine. However, many of these same advantages are included as disadvantages to the use of heparin. Heparin requires an adequate concentration of its cofactor antithrombin III (AT3) in order to inhibit coagulation.² As a result of its size, and its necessary association with AT3, heparin only inhibits fluid-phase thrombin, not clot-bound thrombin.

Heparin resistance

Patients on preoperative heparin therapy traditionally require larger heparin doses to achieve a given level of anticoagulation when anticoagulation is measured by the activated coagulation time (ACT). Presumably this "heparin resistance" is due to deficiencies in the level or activity of AT3.³ Other possible etiologies include enhanced factor VIII activity and platelet activation causing a blunted ACT response to heparin.^{4,5} Montes and Levy have shown that the *in vitro* addition of AT3 enhances the ACT response to heparin.⁶ Lemmer demonstrated that heparin resistance, as measured by the ACT, does not correlate with low preoperative AT3 levels.⁷ It is unclear if these patients have increased heparin requirements during CPB since the ideal ACT and monitoring techniques in heparin-exposed patients have yet to be elucidated.⁸ AT3 concentrate is now available and represents a reasonable method of treating patients with documented AT3 deficiency.

Heparin activates platelets, rendering them aberrantly adhesive, yet less functional in performing normal hemostasis activities.⁹ The mere pro-aggregatory activity of heparin causes a mild reduction in platelet count. This often leads to the clinical syndrome "heparin-induced thrombocytopenia (HIT) type I." This fairly benign process usually occurs early in the course of heparin exposure and is characterized by a mildly reduced platelet count. In contrast, HIT II is an

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immunologically mediated process and is a more serious disease. The platelet surface contains platelet-factor (PF) 4, to which heparin binds. In certain patients, this heparin-PF4 complex generates an immune response and results in the clinical syndrome HIT II.

The heparin/PF4 complexes exist on platelets and endothelial cells and are activated when antibody binds. Associated immune-mediated endothelial injury and complement activation cause platelets to adhere, aggregate, and form platelet clots, or "white clots." Among patients developing HIT II, the incidence of thrombotic complications approximates 20%, which in turn may carry a mortality rate as high as 40%. Demonstration of heparin-induced pro-aggregation of platelets confirms the diagnosis of HIT type II. This can be accomplished with a heparin-induced serotonin release assay, or a specific heparin-induced platelet activation assay. A highly specific enzyme-linked immunosorbent assay for the heparin/PF4 complex has been developed and has been used to delineate the course of IgG and IgM antibody responses in patients exposed to unfractionated heparin during cardiac surgery.

The risks and appropriate courses of action in patients with HIT II are unclear because the antibodies associated with HIT often become undetectable several weeks after discontinuing heparin.¹⁰ Also the clinical syndrome does not always recur upon re-exposure to the drug and sometimes resolves despite continued drug therapy. Many patients never develop thrombosis and disseminated intravascular coagulation despite positive laboratory testing. HIT should possibly be considered in the differential diagnosis of intraoperative heparin resistance in patients receiving preoperative heparin therapy.

The options for treating these patients are few. If one has the luxury of being able to discontinue the heparin for a few weeks, often the antibody will disappear and allow a brief period of heparinization for CPB without complication.^{10,11} Changing the tissue source of heparin might avert the reaction since it may occur more frequently with bovine heparin. Some types of low molecular weight heparin (LMWH) have proven effective in HIT but reactivity of the particular LMWH with the patient's platelets should be confirmed *in vitro*. Supplementing heparin administration with pharmacologic platelet inhibition using prostacyclin, iloprost, aspirin, or aspirin and dipyridamole, and recently, tirofiban, have been reported, with favourable outcomes. Plasmapheresis may be used to reduce antibody levels. The use of heparin could be avoided altogether by anticoagulating with hirudin or bivalirudin.

Hirudin

A coagulation inhibitor isolated from the salivary glands of the medicinal leech (*Hirudo medicinalis*), hirudin is a potent inhibitor of thrombin that, unlike heparin, acts independently of AT3 and inhibits clot-bound thrombin as well as fluid-phase thrombin. Hirudin does not require a co-factor and is not susceptible to neutralization by PF4. It also does not activate platelets as unfractionated heparin does. This would seem beneficial in patients in whom platelet activation and thrombosis is a hallmark of the disease. When used during CPB, hirudin can be given as 0.25 mg·kg⁻¹ bolus and an infusion to maintain the hirudin concentration at 2.5 µg·mL⁻¹ as determined by ecarin clotting time. The ecarin clotting time, modified for use in the Bayer Rapidpoint® analyzer has been used in large series of HIT patients.¹² Compared with standard treatment with heparin or LMWHs, hirudin treated patients maintain platelet counts and hemoglobin levels and have few bleeding complications, if renal function is normal. Hirudin is a small molecule (MW 7kD) that is eliminated by the kidney and is easily filtered at the end of CPB.

Bivalirudin

Bivalirudin is a small 20-amino acid molecule with a plasma half-life of 24 min. It is a synthetic derivative of hirudin and thus acts as a direct thrombin inhibitor. Bivalirudin binds to both the catalytic binding site and the anion-binding exosite on fluid phase and clot-bound thrombin. The part of the molecule that binds to thrombin is actually cleaved by thrombin itself, so the elimination of bivalirudin activity is independent of specific organ metabolism. Bivalirudin has been used successfully as an anticoagulant in interventional cardiology procedures as a replacement for heparin therapy. A series of patients undergoing coronary artery bypass grafting, both on pump and off-pump have also received bivalirudin for safe anticoagulation.^{13,14} Monitoring of anticoagulant activity is performed using the ecarin clotting time with similar prolongation as that seen with hirudin anticoagulation.¹⁵

Antiplatelet therapeutics

The glycoprotein IIb/IIIa (GPIIb/IIIa) receptor is responsible for mediating platelet-platelet aggregation via fibrinogen bridging. Drugs that inhibit this receptor in a reversible or an irreversible fashion are potent inhibitors of platelet aggregation and include abciximab (Reopro®), eptifibatide (Integrilin®), and tirofiban (Aggrastat®). They are frequently infused to prevent thrombus formation in patients who have undergone a high risk coronary interventional proce-

ture. Large-scale multicentre studies have shown that re-thrombosis and infarction rates after percutaneous angioplasty and after stent procedures have been reduced with the use of these drugs.¹⁶ Reductions in mortality and re-infarction rates have been shown in such patient groups as diabetics and patients with prior cardiac surgery.^{17,18}

Of the three *iv* GPIIb/IIIa inhibitors, abciximab is a large monoclonal antibody which binds and causes permanent dysfunction of the GPIIb/IIIa receptor, while also blocking other receptors due to its large size. Comparative studies and head-to-head comparisons have shown that abciximab is superior to the other agents in preventing ischemic complications, which explains its prevalence of use.¹⁹ However, its potent platelet inhibiting properties also render it likely to cause increased episodes of major bleeding. Patients who present for cardiac surgery after having received abciximab often require a prolonged operative time to achieve hemostasis and have an increased incidence of platelet transfusions.²⁰ By contrast, the small molecule agents, eptifibatid and tirofiban are competitive blockers whose small size and half-life of approximately two hours, make it possible to conduct cardiac surgery without an increased risk of bleeding. Studies have documented lower myocardial infarction rates²¹ and similar bleeding rates²² in emergency coronary bypass patients who received eptifibatid compared with those that received placebo prior to surgery. Animal platelet studies suggest that platelets that are quiescent during CPB due to GPIIb/IIIa receptor blockade have better recovery of platelet function after CPB.²³

Antiplatelet therapy has been rapidly advancing due to the introduction of the thienopyridine derivatives ticlopidine and clopidogrel (Plavix®). Clopidogrel has almost completely replaced ticlopidine for this use as it has a wider therapeutic index, a lesser side effect profile, and is more efficacious at doses used clinically. These drugs act by non-competitive antagonism at one of the platelet adenosine diphosphate (ADP) receptors, the P2Y₁₂ receptor. There are three known ADP receptor subtypes. The P2X receptor is a calcium ion channel. The P2Y₁ receptor is the major receptor responsible for regulating calcium influx and subsequent aggregation. The P2Y₁₂ receptor inhibits cyclic adenosine monophosphate production and potentiates platelet aggregation (Figure).

The duration of antiplatelet activity is the life-span of the platelet because the P2Y₁₂ receptor is permanently altered. The effects of clopidogrel plus aspirin are additive and sometimes synergistic depending on the model of platelet function studied. This may

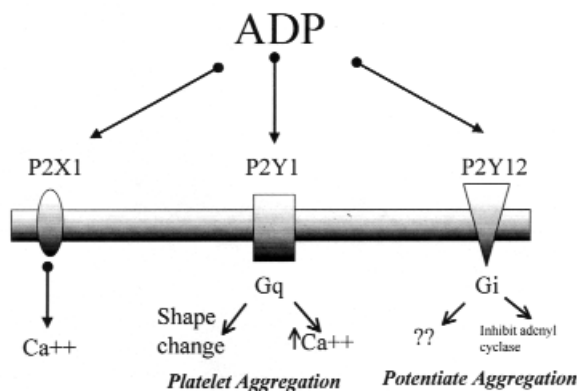


FIGURE The platelet adenosine diphosphate (ADP) receptor sub-types. P2X₁ is a calcium ion channel. P2Y₁ is the major ADP receptor by which shape change, calcium influx, and platelet aggregation occur. Stimulation of the P2Y₁₂ receptor causes reduced levels of camp which potentiates aggregation. Both P2Y receptors are G-protein linked receptors. The thienopyridine drugs clopidogrel and ticlopidine inhibit the P2Y₁₂ receptor in a non-competitive fashion and thus cause rapid de-aggregation.

explain why cardiac surgical patients having received this combination of drugs seem to have excessive post-operative bleeding.²⁴ Patients who are receiving these medications who then present for cardiac surgery are at increased risk for bleeding complications and have a documented increase in transfusions and reoperations for bleeding.^{25,26}

Specific monitoring of the platelet defect induced by these antithrombotic drugs would be advantageous for a number of reasons. For therapeutic efficacy, the degree to which patients are protected from thrombotic events is related to the degree of platelet inhibition.²⁷ Thus platelet function monitoring can be used for titrating drug effect. Alternatively, patients taking these medications who present for surgery can be assayed for their degree of platelet dysfunction and their risk of bleeding and need for transfusion.

Platelet function monitoring

The most critical aspect of monitoring platelet function is the ability to measure the specific defect that is present. Platelet function is so complex, involving multiple pathways of activation, degranulation, cell-signaling pathways, and aggregation, that the proper agonist and end result must be measured if an accurate assessment of platelet function or dysfunction will be made. The following platelet function monitors have

been studied for use in measuring the platelet defect in patients receiving antiplatelet medication. The platelet function analyzer (PFA-100, Dade-Behring, Dade, FL, USA) is an *in vitro* bleeding time that uses a collagen-coated membrane activated with ADP or epinephrine to measure platelet function at the point of care. By virtue of utilizing ADP as an agonist, the PFA-100 would seem useful in measuring platelet dysfunction induced by clopidogrel. It has been used in this fashion in interventional cardiology patients, but does not yet have the predictive capacity of a gold standard like aggregometry.

Ultegra® (Accumetrics, San Diego, CA, USA) is a point of care aggregometer that utilizes fibrinogen macrobeads and a thrombin agonist to activate platelets. When platelets become activated with thrombin, the GPIIb/IIIa receptor is up-regulated and platelet to platelet aggregation via fibrinogen bridging occurs. In the Ultegra®, this bridging occurs via the fibrinogen macrobeads. The degree of agglutination is then measured using optical densitometry methods. When the GPIIb/IIIa receptor is antagonized, the degree to which platelets aggregate is reduced and an appropriate reduction in the Ultegra® platelet function is measured. Ultegra® and the Clot Signature Analyzer (CSA®; Xylum Corp.) have been used to comparatively assess the platelet inhibitory capacity of the three *in vivo* GPIIb/IIIa inhibitors. This study indicated that Ultegra® results were very close to those of standard aggregometry, while the CSA results were unable to detect platelet inhibitory capacity with any specificity.²⁸ High degrees of platelet inhibition on Ultegra®²⁷ have been shown to correlate with a lower incidence of adverse cardiac events after coronary interventions.

PlateletWorks (Helena, Beaumont, TX, USA) assesses platelet function using a platelet count ratio: the ratio of the unactivated platelet count to that in response to a platelet agonist. The reduction in platelet count after the addition of a platelet agonist (ADP, collagen) is directly related to the platelet function. In other words, a larger reduction in platelet count would indicate better platelet function, and *visa versa*. PlateletWorks has been used to assess the inhibition of platelet function in patients taking clopidogrel. The metabolism of clopidogrel to its active drug form is by cytochrome P450 A3. Other drugs that compete for this enzyme will reduce the effectiveness of clopidogrel as a platelet antagonist.^{29,30} This has been documented using the PlateletWorks instrument and with whole blood aggregometry techniques.³¹

Currently, there are no data that validate any point-of-care test as a gold standard measure of platelet

function in patients taking thienopyridine antiplatelet agents. Results with the aforementioned devices have yielded inconsistent results and are considered preliminary investigations. The clinical history of the patient is an excellent indicator of efficacy of the oral antiplatelet agents. This history in conjunction with platelet-rich plasma aggregometry will yield the most reliable data in terms of bleeding risk during surgery or interventional procedures. Similarly, the performance of conduction anesthesia techniques³² should only be performed in patients exposed to the thienopyridine antiplatelet drugs if the drugs have been discontinued for seven to 14 days OR if a proven acceptable test of platelet function yields a normal result. Remember that the appropriate test of platelet function will differ based upon the platelet defect incurred. Different clinical scenarios and different drug regimens will almost certainly dictate different “gold standard” tests of platelet function or dysfunction. It is important to understand the platelet defect present so that the most appropriate testing platform may be selected.

References

- 1 *Hirsh J, Raschke R, Warkentin TE, Dalen JE, Deykin D, Poller L.* Heparin: mechanism of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety. *Chest* 1995; 108: 258S–75S.
- 2 *Levy JH.* Pharmacologic preservation of the hemostatic system during cardiac surgery. *Ann Thorac Surg* 2001; 72: S1814–20.
- 3 *Dietrich W, Diltz G, Spannagl M, Richter JA.* Warfarin pretreatment does not lead to increased bleeding tendency during cardiac surgery. *J Cardiothorac Vasc Anesth* 1995; 9: 250–4.
- 4 *Shore-Lesserson L, Manspeizer HE, Bolastig M, Harrington D, Vela-Cantos F, DePerio M.* Anticoagulation for cardiac surgery in patients receiving preoperative heparin: use of the high-dose thrombin time. *Anesth Analg* 2000; 90: 813–8.
- 5 *Koster A, Fischer T, Gruendel M, et al.* Management of heparin resistance during cardiopulmonary bypass. The effect of five different anticoagulation strategies on hemostatic activation. *J Cardiothorac Vasc Anesth* 2003; 17.
- 6 *Montes FR.* Can we alter heparin dose-responses with antithrombin III? *Anesth Analg* 1996; 82: 94 (abstract).
- 7 *Lemmer JH Jr, Despotis GJ.* Antithrombin III concentrate to treat heparin resistance in patients undergoing cardiac surgery. *J Thorac Cardiovasc Surg* 2002; 123.
- 8 *Nicholson SC, Keeling DM, Sinclair ME, Evans RD.* Heparin pretreatment does not alter heparin require-

- ments during cardiopulmonary bypass. *Br J Anaesth* 2001; 87.
- 9 *Aggarwal A, Sobel BE, Schneider DJ*. Decreased platelet reactivity in blood anticoagulated with bivalirudin or enoxaparin compared with unfractionated heparin: implications for coronary intervention. *J Thromb Thrombolysis* 2002; 13: 161–5.
 - 10 *Warkentin TE, Kelton JG*. Temporal aspects of heparin-induced thrombocytopenia. *N Engl J Med* 2001; 344.
 - 11 *Warkentin TE*. Heparin-induced thrombocytopenia and the anesthesiologist. *Can J Anesth* 2002; 49.
 - 12 *Koster A, Hansen R, Grauhan O, et al*. Hirudin monitoring using the TAS ecarin clotting time in patients with heparin-induced thrombocytopenia type II. *J Cardiothorac Vasc Anesth* 2000; 14.
 - 13 *Davis Z, Anderson R, Short D, Garber D, Valgiusti A*. Favorable outcome with bivalirudin anticoagulation during cardiopulmonary bypass. *Ann Thorac Surg* 2003; 75: 264–5.
 - 14 *Vasquez JC, Vichiendilokkul A, Mahmood S, Baciiewicz FA Jr*. Anticoagulation with bivalirudin during cardiopulmonary bypass in cardiac surgery. *Ann Thorac Surg* 2002; 74: 2177–9.
 - 15 *Koster A, Chew D, Grundel M, Bauer M, Kuppe H, Spiess BD*. Bivalirudin monitored with the ecarin clotting time for anticoagulation during cardiopulmonary bypass. *Anesth Analg* 2003; 96.
 - 16 *Azar RR, McKay RG, Thompson PD, et al*. Abciximab in primary coronary angioplasty for acute myocardial infarction improves short- and medium-term outcomes. *J Am Coll Cardiol* 1998; 32.
 - 17 *Bhatt DL, Marso SP, Lincoff AM, Wolski KE, Ellis SG, Topol EJ*. Abciximab reduces mortality in diabetics following percutaneous coronary intervention. *J Am Coll Cardiol* 2000; 35: 922–8.
 - 18 *Bhatt DL, Topol EJ*. Current role of platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes. *JAMA* 2000; 284: 1549–58.
 - 19 *Brown DL, Fann CS, Chang CJ*. Meta-analysis of effectiveness and safety of abciximab versus eptifibatid or tirofiban in percutaneous coronary intervention. *Am J Cardiol* 2001; 87.
 - 20 *Lemmer JH Jr*. Clinical experience in coronary bypass surgery for abciximab-treated patients. *Ann Thorac Surg* 2000; 70.
 - 21 *Dyke CM, Bhatia D, Lorenz TJ, et al*. Immediate coronary artery bypass surgery after platelet inhibition with eptifibatid: results from PURSUIT. Platelet Glycoprotein IIb/IIIa in Unstable Angina: receptor suppression using integrilin therapy. *Ann Thorac Surg* 2000; 70.
 - 22 *Bizzarri F, Scolletta S, Tucci E, et al*. Perioperative use of tirofiban hydrochloride (Aggrastat) does not increase surgical bleeding after emergency or urgent coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2001; 122.
 - 23 *Suzuki Y, Hillyer P, Miyamoto S, et al*. Integrilin prevents prolonged bleeding times after cardiopulmonary bypass. *Ann Thorac Surg* 1998; 66.
 - 24 *Herbert JM, Dol F, Bernat A, Falotico R, Lale A, Savi P*. The antiaggregating and antithrombotic activity of clopidogrel is potentiated by aspirin in several experimental models in the rabbit. *Thromb Haemost* 1998; 80.
 - 25 *Hongo RH, Ley J, Dick SE, Yee RR*. The effect of clopidogrel in combination with aspirin when given before coronary artery bypass grafting. *J Am Coll Cardiol* 2002; 40.
 - 26 *Merritt JC, Bhatt DL*. The efficacy and safety of perioperative antiplatelet therapy. *J Thromb Thrombolysis* 2002; 13.
 - 27 *Steinhubl SR, Talley JD, Braden GA, et al*. Point-of-care measured platelet inhibition correlates with a reduced risk of an adverse cardiac event after percutaneous coronary intervention: results of the GOLD (AU-Assessing Ultegra) multicenter study. *Circulation* 2001; 103.
 - 28 *Simon D, Liu C, Ganz P, et al*. A comparative study of light transmission aggregometry and automated bedside platelet function assays in patients undergoing percutaneous coronary intervention and receiving abciximab, eptifibatid, or tirofiban. *Catheter Cardiovasc Interv* 2001; 52: 425–32.
 - 29 *Saw J, Steinhubl SR, Berger PB, et al*. Lack of adverse clopidogrel-atorvastatin clinical interaction from secondary analysis of a randomized, placebo-controlled clopidogrel trial. *Circulation* 2003; 108: 921–4.
 - 30 *Wienbergen H, Gitt AK, Schiele R, et al*. Comparison of clinical benefits of clopidogrel therapy in patients with acute coronary syndromes taking atorvastatin versus other statin therapies. *Am J Cardiol* 2003; 92: 285–8.
 - 31 *Lau W, Waskell LA, Watkins PB, et al*. Atorvastatin reduces the ability of clopidogrel to inhibit platelet aggregation: a new drug-drug interaction. *Circulation* 2003; 107: 32–7.
 - 32 *Horlocker T, Wedel DJ, Benzon H, et al*. Regional anesthesia in the anticoagulated patient: defining the risks (the second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). *Reg Anesth Pain Med* 2003; 28: 172–97.