Bivalirudin utilization in cardiac surgery: shifting anticoagulation from indirect to direct thrombin inhibition

Utilisation de la bivalirudine en chirurgie cardiaque – de l’inhibition indirecte à l’inhibition directe de la thrombine

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Abstract

Purpose Bivalirudin use for anticoagulating patients undergoing cardiac surgery, particularly those with or at risk for heparin-induced thrombocytopenia, has expanded over the past several years. The purpose of this review is to provide a summary of the following: the differences between indirect and direct thrombin inhibition, unfractionated heparin’s limitations (i.e., heparin-induced thrombocytopenia), bivalirudin’s pharmacology, recent cardiac surgery trials comparing bivalirudin and unfractionated heparin as anticoagulants, the growing role of bivalirudin-mediated anticoagulation for various surgical procedures, and the potential of bivalirudin-mediated vascular graft patency.

Source A systematic search of the English literature was performed using PubMed from the United States National Library of Medicine. Pertinent articles from 1992–2010 were obtained from this search, and their reference lists were used to retrieve additional relevant articles.

Principal findings In small studies in the cardiac surgery arena, bivalirudin has demonstrated a similar safety and efficacy profile compared with unfractionated heparin. Bivalirudin’s role as an anticoagulant in various cardiac surgical procedures (i.e., heart transplant) and vascular surgical procedures is growing and reviewed. Additionally, the molecular basis for the potential for bivalirudin-mediated improvement in vascular graft patency after coronary artery bypass graft procedures is discussed.

Conclusion Although bivalirudin is not approved for cardiac surgery in the United States, it can be used in this setting in Canada as an anticoagulant in patients with heparin-induced thrombocytopenia provided the cardiac anesthesiologist is knowledgeable about potential complications from its use and knows how to manage or mitigate their incidence appropriately. During cardiopulmonary bypass, bivalirudin anticoagulation protocols must be thoroughly followed to attain optimal clinical outcomes. Additionally, further studies with bivalirudin are needed to determine the best monitoring modality and dosing regimen.

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Résumé

Objectif L’utilisation de la bivalirudine chez les patients sous anticoagulants devant subir une chirurgie cardiaque, et plus particulièrement chez ceux qui présentent une thrombocytopénie induite par l’héparine ou qui en courent le risque, s’est répandue au cours des dernières années. Cet article de synthèse offre un aperçu des différences entre l’inhibition indirecte et l’inhibition directe de la thrombine, des limitations de l’héparine non fractionnée (p. ex. la thrombocytopénie induite par l’héparine), de la pharmacologie de la bivalirudine, de récentes études en chirurgie cardiaque comparant la bivalirudine et l’héparine non fractionnée en tant qu’anticoagulants, du

rôle croissant de l'anticoagulation facilitée par la bivalirudine lors de diverses interventions chirurgicales et du potentiel d'amélioration facilitée par la bivalirudine de la perméabilité du greffon vasculaire.

Source Une recherche systématique de la littérature rédigée en anglais a été effectuée sur PubMed à partir de la United States National Library of Medicine et a permis d'obtenir des articles pertinents datés de 1992 à 2010. Les listes de références de ces articles ont ensuite été utilisées pour accéder à d'autres articles pertinents.

Constatations principales Dans le cadre d'études de faible envergure, la bivalirudine a démontré un profil d'innocuité et d'efficacité similaire à celui de l'héparine non fractionnée lors d'une chirurgie cardiaque. Le rôle de la bivalirudine en tant qu'anticoagulant utilisé lors de diverses interventions chirurgicales cardiaques (p. ex. transplantation cardiaque) et vasculaires prend de l'ampleur et est de plus en plus étudié. Nous présentons également les mécanismes au niveau moléculaire qui sous-tendent le potentiel d'amélioration facilitée par la bivalirudine de la perméabilité du greffon vasculaire après une chirurgie de pontage aorto-coronarien.

Conclusion Bien que la bivalirudine ne soit pas approuvée pour la chirurgie cardiaque aux États-Unis, elle peut être utilisée comme anticoagulant au Canada chez les patients présentant une thrombocytopénie induite par l'héparine, pourvu que l'anesthésiologiste cardiaque connaisse les complications pouvant résulter de son utilisation et soit en mesure de les gérer ou de limiter leur incidence. Les protocoles d'anticoagulation par la bivalirudine lors d'une circulation extra-corporelle doivent être strictement respectés afin d'obtenir les meilleurs résultats cliniques possibles. En outre, on doit encore étudier la bivalirudine en vue de déterminer les modalités de monitoring et les schémas posologiques les plus efficaces.

The anticoagulation strategy implemented during cardiac surgery is important with respect to overall perioperative outcome. Traditionally, unfractionated heparin (UFH) has been utilized as the primary anticoagulant for cardiac surgery involving valve replacement and/or vessel revascularization performed with cardiopulmonary bypass (CPB) or off-pump coronary artery bypass (OPCAB). Unfractionated heparin, an indirect thrombin inhibitor, has served this purpose since the onset of modern day cardiac surgery due, in part, to its immediate reversibility with protamine. However, both heparin and protamine have inherent limitations, often with potentially deleterious clinical consequences, e.g., heparin-induced thrombocytopenia (HIT) or protamine-mediated cardiopulmonary/circulatory perturbations (e.g., anaphylaxis, peripheral

vasodilatation, pulmonary vasoconstriction, or noncardiogenic pulmonary edema).¹ Hemodynamic instability after protamine administration to reverse UFH during CPB has been reported to be associated with a 13.2% same hospital admission mortality rate.² These untoward sequelae have compelled basic science and clinical investigators to search for alternate anticoagulation strategies. Bivalirudin, a direct thrombin inhibitor, has been evaluated recently in several cardiac surgery trials. This review compares the clinical and biochemical features of indirect and direct thrombin inhibitors (DTI) and summarizes the following: the limitations of UFH, including HIT; bivalirudin's pharmacology; monitoring strategies for DTIs; recent clinical trials comparing bivalirudin with UFH in HIT-positive or HIT-negative patients undergoing cardiac surgery with or without CPB; the emerging role of bivalirudin-mediated anticoagulation in the perioperative period; and the theoretical considerations of bivalirudin-mediated vascular graft patency.

Indirect vs direct thrombin inhibition

Of the myriad of proteins involved in the coagulation cascade, it is arguably the serine protease thrombin that plays the pivotal role in modulating thrombus formation and the global hemostatic process. Reasonably then, inhibiting thrombin generation or activity has been the focus of many pharmacologic interventions. Indirect thrombin inhibition involves the use of a catalyst, UFH, which potentiates the activity of endogenous anticoagulants, specifically antithrombin (AT) III.³ Inhibition of the hemostatic system via UFH involves several different mechanisms. Unfractionated heparin inhibits coagulation proteins via a unique pentasaccharide sequence that binds to AT III and markedly increases the affinity of AT III-mediated inactivation of thrombin and factors IXa, Xa, XIa, and XIIa (Fig. 1).⁴ Thus, indirect thrombin inhibition with UFH proximally attenuates thrombin generation by coagulation factor inhibition and indirectly attenuates thrombin activity via AT III. However, inhibition of thrombin occurs predominantly with higher molecular weight fractions of UFH that consist of longer polysaccharide units (> 18-20). Unfractionated heparin also inhibits the hemostatic system via release of tissue factor pathway inhibitor,⁵ which results in inhibition of contact activation⁶ and, in the majority of patients, probably directly or indirectly inhibits platelet function, especially when higher plasma concentrations (> 3-4 U·mL⁻¹) are achieved.⁷⁻¹¹ This inhibition may be mediated via attenuation of collagen-mediated aggregation,^{7,8} factor VIII-associated platelet aggregation,¹¹ or von Willebrand factor-related mechanisms.¹⁰ Although low concentrations

Fig. 1 Schematic representation of the coagulation cascade with bivalirudin and heparin inhibition targets. Bivalirudin inhibits factor IIa (thrombin). Heparin potentiates antithrombin III-mediated inhibition of factors IIa, IXa, Xa, XIa, and XIIa. Modified from Anaesthesia UK, www.frca.co.uk

of UFH do not effectively inhibit thrombin bound to fibrin, this can be overcome if higher concentrations are achieved¹² during CPB. High UFH concentrations (4–5 U·mL⁻¹) can suppress thrombin activity,^{13,14} preserve coagulation factors¹³ and platelet count,¹⁵ and result in less bleeding and fewer transfusions.¹⁶ In contrast, direct thrombin inhibition does not involve a catalyst; the inhibition is mediated without AT III and involves a thrombin-direct antagonist interaction. The DTIs, hirudin, bivalirudin, and argatroban, all bind thrombin at one of several sites resulting in attenuation of its activity (Fig. 1).¹⁷ Furthermore, direct thrombin inhibition also prevents thrombin generation by another pathway, i.e., by inhibiting platelet activation¹⁸ and thus the catalytic phospholipid surface on which the coagulation factors propagate themselves. Advantages of direct thrombin inhibition compared with indirect thrombin inhibition include no plasma protein binding, lack of reliance on AT III and therefore a more reliable anticoagulant response (i.e., AT III deficiency), and the ability to mitigate the thrombogenic potential of thrombin bound to clot.¹⁷

Limitations of unfractionated heparin

Unfractionated heparin is a highly anionic heterogeneous mixture of sulfated and carboxylated glycosaminoglycans derived from bovine lung or porcine intestine (Fig. 2).¹⁹ Unfractionated heparin contains a pentasaccharide sequence that induces a conformational change in AT III potentiating its inhibition of thrombin (Fig. 1) and factors IXa, Xa, XIa, and XIIa²⁰ to promote anticoagulation. Although used for more than 70 years in a myriad of clinical settings, UFH has well-known limitations. Unfractionated heparin binds non-specifically to plasma proteins and endothelial cells which results in a variable anticoagulant response, particularly in the critically ill population.^{21–23} Furthermore, UFH initiates its own negative feedback loop by activating platelets,¹⁸ causing the release of UFH neutralizing proteins, such as platelet factor 4 (PF4) and von Willebrand factor. Binding of these proteins to UFH may result in resistance necessitating administration of higher doses of UFH.²⁴ In addition, UFH is unable to attenuate clot-bound thrombin at lower concentrations,^{12,25} thrombin bound to soluble fibrin degradation

Fig. 2 a Schematic representation of heparin.
b General view of the crystal structure of the ternary complexes between antithrombin (violet ribbon), thrombin (green ribbon), and heparin (red, grey, orange space-filling model). Ser = Serine. Modified with permission from *Imberty A, Lortat-Jacob H, Perez S*. Structural view of glycosaminoglycan-protein interactions. *Carbohydr Res* 2007; 342: 430-9

products²⁶ or subendothelial extracellular matrix,²⁷ and activated platelet-bound factor Xa,²⁸ thus allowing for more active thrombin generation.¹² Ineffective suppression of thrombin in turn may lead to thrombin-mediated platelet activation²⁹ and the possibility of thrombus propagation at the site of vascular injury. Further, UFH demonstrates a non-linear half-life due to bimodal clearance via endothelial cells/macrophage endocytosis first and then by renal elimination. However, this is generally not an issue since protamine is utilized to reverse the anticoagulant effects of heparin immediately via rapid ionic binding and clearance via the reticuloendothelial system.³ An important limitation deserving focused attention is the potential formation of anti-PF4/UFH antibodies and, more importantly, HIT-related thrombotic complications.³⁰

Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia is a potentially lethal condition that manifests in 1-3% of patients after UFH administration and development of anti-PF4/UFH antibodies³¹ (Fig. 3). The disorder is characterized by a platelet count $< 150,000 \cdot \text{mL}^{-3}$ or a 30-50% decrease from baseline after UFH exposure.³² Moreover, thrombotic complications (e.g., limb ischemia) occur in 20-50%³³⁻³⁶ of

HIT patients and consequent amputation in 5-10%,^{37,38} with arterial thrombosis predominating³¹ and a 28% mortality rate³⁹ in cardiac surgery patients, warrants UFH discontinuation from all sources and necessitates implementation of an alternative anticoagulation strategy. The diagnosis of HIT in cardiac surgery patients thus presents a conundrum. These patients often present with angina pectoris, are found to have myocardial ischemia requiring surgical coronary revascularization, and are started on an anticoagulant, namely intravenous (IV) UFH, to abrogate thrombotic risk. If HIT develops in this clinical scenario, UFH needs to be replaced and often is replaced with a DTI (i.e., bivalirudin). Recently, bivalirudin has been the focus of many basic science and clinical studies to determine its pleiotropic effects and to outline its safety and efficacy in acute coronary syndromes and in percutaneous and surgical cardiac interventions.

Bivalirudin history and pharmacology

The search for alternative agents was initially predicated on the reduced ability of therapeutic doses of UFH to inhibit clot-bound thrombin.¹² Bivalirudin, a synthetic dodecapeptide bivalent DTI, has its history rooted with that of hirudin, a natural irreversible bivalent DTI, derived from

Fig. 3 **a** Schematic representation of the interaction of HIT-IgG with platelets. In Panel A, platelet factor 4 (PF4) is released from platelet α -granules after platelet activation. The PF4 binds to the platelet surface through glycosaminoglycans (GAGs) that are associated with tetramers of PF4. Panel **b** shows heparin binding to the PF4. The size of the PF4 bundle is related, in part, to the chain length of the heparin. Panel **c** shows HIT-IgG binding to epitopes on the PF4-heparin

complex. Panel **d** shows ultra-large complexes (ULC) of heparin/PF4 and IgG binding to platelets via the platelet FcR γ IIa. The immune complexes are potent platelet activators leading to the release of platelet-derived procoagulant microparticles. Used with permission from Kelton JG, Warkentin T. Heparin-induced thrombocytopenia: a historical perspective. *Blood* 2008; 112: 2607-17

the salivary glands of the medicinal leech, *Hirudo medicinalis*.⁴⁰ Isolation of hirudin, description of its antithrombotic effects and discovery of its sequence, structure and recombinant forms have occurred over the past 125 years.⁴⁰ Hirudin has been found to be the most potent natural inhibitor of thrombin and has been studied in numerous clinical trials, eventually leading to regulatory approval for its recombinant form.⁴¹ Bivalirudin, previously known as HirulogTM, was developed by Biogen as a synthetic form of hirudin that incorporates the binding affinity to both the catalytic active site and the anion-binding exosite of thrombin.⁴² Currently, bivalirudin is manufactured by The Medicines Company at a cost of approximately \$325 USD for a 250 mg vial.⁴³

Bivalirudin was initially studied in an uncontrolled, multicentre, open-label dose-determination trial of 279 patients who were undergoing percutaneous transluminal coronary angioplasty (PTCA).⁴⁴ Data from this trial suggested that the higher bivalirudin dosage regimens of 1.8–2.2 mg·kg⁻¹·hr⁻¹ infusions may be comparable with UFH during PTCA and that further study was warranted.⁴⁴ The

Hirulog Angioplasty Study (HAS) was a multicentre, controlled, randomized, double-blind investigation involving 4,098 patients undergoing urgent PTCA for unstable angina who were thrombolytic therapy naïve in the previous 24 hr.⁴⁵ All patients received aspirin 300–325 mg and were randomized either to bivalirudin 1 mg·kg⁻¹ bolus plus 2.5 mg·kg⁻¹·hr⁻¹ infusion for four hours followed by a 0.2 mg·kg⁻¹·hr⁻¹ infusion for 14–20 hr or to UFH 175 U·kg⁻¹ bolus followed by a 15 U·kg⁻¹·hr⁻¹ infusion for 18–24 hr with 60 U·kg⁻¹ supplement boluses if the activated clotting time (ACT) was < 350 sec.⁴⁵ The primary endpoint was a composite of death, myocardial infarction (MI), abrupt coronary closure, or urgent revascularization during hospitalization.⁴⁵ The original analysis revealed that bivalirudin did not reduce the composite endpoint compared with UFH (11.4% vs 12.2%, respectively; $P = 0.44$) but reduced the major bleeding incidence (3.8% vs 9.8%, respectively; $P < 0.001$).⁴⁵ The Bivalirudin Angioplasty Trial (BAT) was the reanalysis of HAS using contemporary definitions of the endpoints and complex analytical analysis. It included 214 enrolled HAS patients on a

per-intention-to-treat basis who had not undergone PTCA.⁴⁶ Reported results from this analysis suggested that bivalirudin was as effective as UFH in reducing ischemic events in unstable angina PTCA patients with marked reduction in major bleeding (composite endpoint of death, MI, revascularization at day 7 was 6.2% vs 7.9%, respectively; $P = 0.039$ and major bleeding 3.5% vs 9.3%, respectively; $P < 0.001$).⁴⁶ Predicated on the BAT findings, the United States Federal Drug Administration (FDA) granted approval for the use of bivalirudin at the HAS dose in unstable angina patients undergoing PTCA.

The Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE-1) trial was a randomized, open-label study of 1,056 patients undergoing elective/urgent percutaneous coronary intervention (PCI), comparing procedural bivalirudin 0.75 mg·kg⁻¹ bolus followed by a 1.75 mg·kg⁻¹·hr⁻¹ infusion to UFH 70 U·kg⁻¹ bolus with operator-determined glycoprotein (GP) IIb/IIIa antagonist.⁴⁷ All patients received aspirin, and use of clopidogrel was encouraged.⁴⁷ Intracoronary stents and GP IIb/IIIa antagonist were used in 85% and 72% of bivalirudin-treated patients, respectively.⁴⁷ The primary endpoint, a composite of death, MI, or urgent revascularization upon hospital discharge or within 48 hr, occurred in 5.6% bivalirudin-treated vs 6.9% UFH-treated patients ($P = 0.40$).⁴⁷ Major bleeding occurred in 2.2% bivalirudin-treated vs 2.7% UFH-treated patients ($P = 0.52$).⁴⁷ Based on the REPLACE-1 results, REPLACE-2 was developed to study procedural bivalirudin 0.75 mg·kg⁻¹ bolus followed by 1.75 mg·kg⁻¹·hr⁻¹ infusion with provisional use of GP IIb/IIIa antagonists (abciximab or eptifibatide, $n = 2,999$) compared with UFH 65 U·kg⁻¹ bolus with planned GP IIb/IIIa antagonists ($n = 3,011$) in a multinational, multicentre, randomized, controlled, double-blind investigation.⁴⁸ The primary composite endpoint was death, MI, urgent repeat revascularization, or in-hospital major bleed at day 30.⁴⁸ Only 7.2% of patients receiving bivalirudin were administered GP IIb/IIIa antagonist, 100% received aspirin, 85% received clopidogrel 300 mg prior to the procedure, and 85.7% had intracoronary stents placed.⁴⁸ At day 30, the primary composite endpoint was seen in 9.2% of bivalirudin-treated patients vs 10.0% of UFH-treated patients ($P = 0.32$).⁴⁸ In-hospital major bleeding rates were reduced with bivalirudin compared to UFH (2.4% vs 4.1%, respectively; $P < 0.001$).⁴⁸ Based on the data from REPLACE-2, the FDA granted approval for the use of bivalirudin as an anticoagulant with provisional GP IIb/IIIa antagonists in patients undergoing PCI.

Bivalirudin has structural analogy to hirudin in that it contains hirudin's functional amino and carboxy terminal groups.⁴² Its unique characteristics include a short half-life (approximately 25 min) and a low proclivity to generate an immune response.⁴⁹ Notably, a recent study demonstrated

Fig. 4 Schematic representation of bivalirudin-bound thrombin. Thrombin has three binding sites. Exosite 1 is the cationic substrate binding site (i.e., fibrinogen, bivalirudin). Exosite 2 is the cationic heparin binding site. The anionic catalytic active site is where bivalirudin binds thrombin and exerts its direct inhibition of the molecule. Proteolytic cleavage occurs at this site changing bivalirudin from a non-competitive inhibitor to a competitive inhibitor, thereby decreasing bivalirudin's affinity for thrombin and allowing functional active site recovery

antilepirudin antibodies cross-reacting with bivalirudin *in vitro*, suggesting the possibility of immune anaphylaxis in cases where previous lepirudin (recombinant hirudin) exposure had occurred followed by bivalirudin exposure.⁵⁰ Bivalirudin binds both clot-bound and fluid-phase thrombin to inhibit thrombin and thereby fibrin formation.⁴⁹ Moreover, thrombin active site function is restored when the arginine-proline bond at the amino-terminal of bivalirudin in thrombin's active site undergoes proteolysis, weakening its carboxy-terminal binding affinity for the anion-binding exosite 1 (Fig. 4).⁴²

Bivalirudin exhibits linear pharmacokinetics when administered intravenously.⁵¹⁻⁵³ Peak bivalirudin plasma concentrations were directly correlated to doses ranging from 0.05-0.6 mg·kg⁻¹ after 15-min IV infusions and were achieved within five minutes of infusion completion.⁵¹ Moreover, bivalirudin steady-state concentrations, measured during 48-hr continuous IV infusions using doses from 0.25-1.0 mg·kg⁻¹·hr⁻¹, were directly correlated to dose.⁵² Furthermore, a steady-state plasma concentration of 4.2 mg·L⁻¹ was demonstrated after a bivalirudin 1 mg·kg⁻¹·hr⁻¹ infusion, but increased to 12.3 mg·L⁻¹ when the dose was a 1 mg·kg⁻¹ bolus followed by a 4-hr 2.5 mg·kg⁻¹·hr⁻¹ infusion.^A In addition, bivalirudin does not bind to plasma proteins and has a 13 L volume of distribution.^B

Bivalirudin elimination is initially predominantly dependent on thrombin active site-mediated proteolytic

^A Product Insert. Angiomax (bivalirudin). Parsippany, NJ: The Medicines Company; 2005.

^B Product Monograph. Angiomax (bivalirudin). Mississauga, Ontario, Canada: Sepracor Pharmaceuticals 2010.

cleavage. Bivalirudin bound to thrombin undergoes cleavage of the amino terminal arginine-proline bond decreasing bivalirudin's affinity for and allowing substrate-mediated displacement from thrombin's exosite 1.¹⁷ Further, bivalirudin is relatively dependent on renal glomerular filtration, independent of hepatic clearance mechanisms, and in the setting of renal dysfunction appropriate when administered with dose adjustment.⁵³ In those patients with moderate renal dysfunction, evidence suggests that the bivalirudin dose should be decreased by 20% in order to compensate for the 20% reduction in plasma clearance.⁵³ Moreover, severe renal function impairment (glomerular filtration rate 10–29 mL·min⁻¹) leads to an approximate doubling in half-life to 57 min compared with those patients with normal renal function (normal half-life 25 min)⁵¹ suggesting a need to reduce the bivalirudin dose from 2.5 to 1 mg·kg⁻¹·hr⁻¹ in this subpopulation.⁵³ With bivalirudin's linear pharmacokinetics, dose adjustments should result in a consistent and proportional response. In addition to dose adjustment, large-pore hemofilters can be utilized for extracorporeal elimination of bivalirudin to attenuate its anticoagulant effect and mitigate hemorrhagic risk after CPB.⁵⁴ Additionally, bivalirudin was recently shown to have clinical outcomes comparable with UFH in chronic dialysis-dependent PCI patients.⁵⁵

Bivalirudin also exhibits a linear dose-response anticoagulant effect. The prothrombin time, activated partial thromboplastin time (aPTT), thrombin time, and ACT all rise linearly with an increase in bivalirudin dose.⁵¹ Further, a bivalirudin dose of 0.2 mg·kg⁻¹·hr⁻¹ increased the prothrombin time from 12–16 sec, aPTT from 27–62 sec, and thrombin time from 15–73 sec.⁵⁶ Moreover, a bivalirudin infusion rate of 1 mg·kg⁻¹·hr⁻¹ resulted in an average aPTT of 98 sec, which returned to baseline within four hours of infusion discontinuation.⁵²

Although selective for thrombin and effectively titratable with rapid onset of action, an antidote has not been formulated for bivalirudin, thereby preventing it from being immediately reversed and potentially increasing the risk of life-threatening hemorrhage with its use. Active reversibility is the cornerstone of anticoagulant therapy during CPB and is a significant reason for using heparin with protamine in this setting, albeit with both agents' limitations.^{1,2,20,31,57,58} A bivalirudin neutralizing agent would provide a possible means for immediate active reversal of anticoagulation as opposed to temporal endogenous metabolic clearance to mitigate bivalirudin's effect perioperatively. Bivalirudin reversibility was demonstrated utilizing a combination of hemodialysis and modified ultrafiltration, recombinant FVIIa, and fresh frozen plasma (FFP)/cryoprecipitate to attenuate non-surgical bleeding after CPB in a heart transplant patient.⁵⁹ It can be surmised, though, that a bivalirudin antidote may be beneficial to

potentially mitigate the observed bleeding that often occurs in complex cardiovascular and vascular procedures.

Monitoring bivalirudin anticoagulation during cardiac surgery

The administration of bivalirudin has demonstrated a dose-response relationship in a number of coagulation tests, including international normalized ratio, aPTT, and ACT.⁵¹ The ACT measures time for whole blood to clot in the presence of Celite® (diatomaceous earth) in a rotating glass specimen tube with a magnet.⁶⁰ As the clot forms, the magnet is displaced from the bottom of the tube activating a switch in the Hemochron® device and registering a clotting time on the display.⁶⁰ In a similar manner to Celite®, kaolin (clay silicate) is used for whole blood contact activation in glass specimen tubes for ACT measurements. During CPB, when heparin and aprotinin (serine protease that inhibits plasmin) are used together, Celite®-ACT values are higher than kaolin-ACT values.⁶¹ This observation is likely due to kaolin adsorption of aprotinin and therefore reflects heparin-mediated anticoagulation alone. In contrast, elevated ACT values with Celite® reflect anticoagulation mediated by both heparin and aprotinin because Celite® does not adsorb aprotinin.^{61,62} The ecarin clotting time (ECT) employs use of the snake venom, ecarin, to generate meizothrombin from prothrombin when added to whole blood containing a DTI.⁶³ Meizothrombin has thrombin-like serine protease activity and will bind with DTI in the blood sample to neutralize it. This allows the remaining free meizothrombin to form clots and thus explains the correlation between DTI plasma concentration and extension of clotting time.⁶³ During cardiac surgery, bivalirudin has been monitored with point-of-care anticoagulation tests, such as the global ACT and meizothrombin specific ECT.^{34,64,65} Both coagulation tests have reasonable correlations with bivalirudin plasma concentration,^{34,66} with the ECT demonstrating a stronger correlation (ECT R² = 0.91 vs ACT_{plus} R² = 0.83)⁶⁶ with therapeutic levels (10–15 µg·mL⁻¹)^{65,66} of bivalirudin during CPB and PCI⁶⁷ (Fig. 5). However, of note, ECT values of 200 sec were associated with a wide range of bivalirudin concentrations (3–8 µg·mL⁻¹).^{67,68} More importantly, these correlations can be ambiguous in the setting of CPB predominately due to the effects of hemodilution (reduction in coagulation factor proteins)¹³ and hypothermia (slow coagulation reaction time and thereby prolonged clotting time) on these coagulation tests.^{69,70} In an attempt to overcome the limitations of these tests with CPB, reagent human plasma has been used with the ECT with some success.⁷¹ Therefore, mixing reagent standard human plasma in a 1:1 dilution with patient whole

Fig. 5 Correlation of thrombin inhibitor management-ECT citrated and ACT with bivalirudin plasma concentration from all samples collected during the study. Modified with permission from *Casserly IP, Kereiakes DJ, Gray WA, et al. Point-of-care ecarin clotting time vs activated clotting time in correlation with bivalirudin concentration. Thromb Res 2004; 113: 115-21.* ECT = ecarin clotting time; ACT = activated clotting time

blood prior to ECT testing should be considered when attempting to monitor DTIs during CPB. Bivalirudin protocols using the ACT to guide dosing during cardiac surgery have been developed for CPB and OPCAB (Tables 1 and 2). Furthermore, in PCI cases using bivalirudin the ACT has been shown to have no correlation with myocardial ischemia and bleeding complications.^{45,46,72,73}

Due to the differences in ACT systems in use and their variable response to bivalirudin, new technologies have developed to improve bivalirudin monitoring during cardiac surgery. Preliminary evidence indicates that the ACTT (a modified ACT with improved clotting time linearity to high bivalirudin concentrations) correlates with low and high plasma concentrations of bivalirudin in this setting.⁷⁴ Additionally, the Thromboelastograph®-based ECT was introduced recently and was found to provide rapid monitoring of bivalirudin during CPB⁷¹; however, this method is

not commercially available in the United States. Notably, neither technology has been studied in large, randomized, controlled trials to gain ubiquitous clinical adoption. The paucity of data regarding this important question necessitates undertaking future investigations to determine the appropriate point-of-care method for monitoring bivalirudin-mediated anticoagulation and to identify ideal dosing regimens based on clotting times to enhance clinical outcomes in the perioperative cardiac surgical setting.

Bivalirudin studies in the cardiac surgical setting

Currently, bivalirudin has a FDA indication for use in PCI patients with or at risk for HIT.⁴⁸ Bivalirudin has not received FDA approval for use in the cardiac surgical arena, but the Canadian Health Protection Branch has recommended its use in patients with HIT or at risk for HIT thrombosis syndrome who are undergoing PCI or cardiac surgery.^B Further, bivalirudin is approved for use in Canada as an anticoagulant in patients undergoing PCI and in the treatment of patients with moderate to high-risk acute coronary syndromes due to unstable angina or non-ST-segment elevation in whom early PCI is planned.^B To evaluate its safety and efficacy compared with UFH, bivalirudin has been studied in small clinical studies in patients with or without HIT undergoing cardiac surgery with or without CPB (Table 3).^{64,66,75-78} Merry *et al.* conducted a multicentre, randomized, unblinded pilot study enrolling 100 OPCAB patients to compare perioperative blood loss between those receiving bivalirudin ($0.75 \text{ mg} \cdot \text{kg}^{-1}$ bolus followed by $1.75 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ infusion) and those receiving UFH ($150\text{--}300 \text{ U} \cdot \text{kg}^{-1}$) with protamine reversal ($1 \text{ mg}:100 \text{ U UFH}$).⁷⁷ Median perioperative blood loss was similar; 793 mL for bivalirudin compared with 805 mL for UFH (interquartile range 320-4,909 mL vs 517-1,117 mL, respectively; $P = 0.165$).⁷⁷ Furthermore, there were similar bleeding rates in both groups, with severe bleeding events occurring in two bivalirudin-treated patients vs no patients treated with UFH and protamine. Additionally, there were significantly more blood product transfusions required in the bivalirudin group (12) compared with the UFH group (9).⁷⁷ Moreover, at a three-month coronary angiography analysis better graft flow grades and patency rates were attributed to bivalirudin than to UFH, owing possibly to bivalirudin's role in abrogating neointimal hyperplasia.⁷⁷

The EVOLUTION-ON trial was a randomized, prospective, multicentre, active-controlled, unblinded underpowered trial in patients undergoing cardiac surgery (primary or reoperative coronary artery bypass graft [CABG] surgery, CABG with valve surgery, or valve surgery alone) with planned CPB who were administered either bivalirudin or

Table 1 Bivalirudin anticoagulation protocol for cardiopulmonary bypass

Pre-CPB bivalirudin dosing: initial bolus and continuous infusion	1.0 mg·kg ⁻¹ body weight bolus + 2.5 mg·kg ⁻¹ ·hr ⁻¹ infusion
Bivalirudin added to pump circuit volume	50 mg
Target bivalirudin plasma concentration	> 10 µg·mL ⁻¹ at CPB start; if < 10 µg·mL ⁻¹ give additional 0.1–0.5 mg·kg ⁻¹ bolus
On-CPB bivalirudin continuous infusion	2.5 mg·kg ⁻¹ ·hr ⁻¹ until 15 min prior to separation from CPB (if CPB not terminated in 20 min, then give a 0.5 mg·kg ⁻¹ bolus + start infusion at 2.5 mg·kg ⁻¹ ·hr ⁻¹)
On-CPB bivalirudin assay monitoring	Every 15–30 min
On-CPB subtherapeutic monitoring assay* value	Give 0.1–0.5 mg·kg ⁻¹ bolus
Discontinue bivalirudin infusion 15 min prior to separation from CPB, then approach (A) After separation from CPB, promptly reconnect arterial and venous lines, clamp out arterial filter, give residual blood to the patient, refill CPB with saline, re-circulate, add bivalirudin 50 mg, and then start an infusion at 50 mg·hr ⁻¹ into the circuit. This volume may be processed later by cell saver for reinfusion or it may be discarded. Approach (B) within 10 min, empty pump volume into cell saving device (replace pump volume with sodium citrate) to eschew post-separation bivalirudin boluses to circuit; process blood for reinfusion into patient with cell saving device to remove bivalirudin.	

* The target bivalirudin concentration ($\sim 10 \mu\text{g}\cdot\text{mL}^{-1}$) corresponds to > 2.5 times baseline increase for the ACT-Kaolin (Hemochron®), ACT-Plus®, ACT-T (International Technidyne), or ecarin clotting time. CPB = cardiopulmonary bypass; ACT = activated clotting time. Modified with permission from Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia and cardiac surgery. *Ann Thorac Surg* 2003; 76: 638–48.

Table 2 Bivalirudin anticoagulation protocol for off-pump cardiopulmonary bypass

Off-CPB bivalirudin dosing: bolus and continuous infusion	0.75 mg·kg ⁻¹ body weight bolus + 1.75 mg·kg ⁻¹ ·hr ⁻¹ infusion
Target ACT > 300 sec	ACT < 300 sec, increase bivalirudin infusion by 0.25 mg·kg ⁻¹ ·hr ⁻¹ or administer 0.1–0.5 mg·kg ⁻¹ bolus

Maintenance infusion discontinued at discretion of surgeon/anesthesiologist often 15 min prior to graft flow restoration.

CPB = cardiopulmonary bypass. ACT = activated clotting time. Modified from Smedira *et al.* Anticoagulation with bivalirudin for off-pump coronary artery bypass grafting: the results of the EVOLUTION-OFF study. *J Thorac Cardiovasc Surg* 2006; 131: 686–92.

UFH with protamine.⁷⁵ A bolus dose of bivalirudin 1 mg·kg⁻¹ was given followed by a 2.5 mg·kg⁻¹·hr⁻¹ infusion.⁷⁵ In addition, bivalirudin 50 mg was added to the CPB pump priming solution.⁷⁵ Unfractionated heparin was administered per institutional protocol averaging an initial bolus of 344 U·kg⁻¹ UFH, a total bolus of 441 U·kg⁻¹ UFH, and a subsequent reversal protamine dose of 3.7 mg·kg⁻¹.⁷⁵ No significant difference between bivalirudin and UFH was evident in the primary endpoint of composite freedom from death, Q-wave MI, stroke, or repeat revascularization at 7, 30, or 84 days (94.9% vs 96.2%, 94.9% vs 94.2%, and 94.8% vs 92.2%, respectively).⁷⁵ Notably, there was a lower percentage (bivalirudin 6.1% vs UFH 11.5%; $P = 0.34$) of perioperative MI at day 7.⁷⁵ Although there was an early median blood loss noted at two hours (bivalirudin 238 mL vs UFH 160 mL; $P = 0.0009$), the 24-hr total blood loss showed no difference between the two arms (bivalirudin 793 mL vs UFH 668 mL; $P = 0.15$).⁷⁵ However, 6 patients treated with bivalirudin had > 2 L of blood loss after surgery while no patients receiving UFH had > 2 L of blood loss.⁷⁵ Although there was no difference in the global transfusion rates between the bivalirudin and UFH cohorts (58.2% vs 59.6%, respectively), more blood product was administered to patients treated with bivalirudin (packed

red blood cells [PRBC] 57.1% vs 51.9%; platelets 19.4% vs 9.6%; FFP 27.6% vs 23.1%, respectively).⁷⁵

The EVOLUTION-OFF study was a multicentre, randomized, unblinded, underpowered trial comparing UFH with protamine reversal to bivalirudin in OPCAB patients.⁷⁸ Bivalirudin was administered at a bolus dose of 0.75 mg·kg⁻¹ followed by a 1.75 mg·kg⁻¹·hr⁻¹ infusion with the option to tailor therapy to a target ACT > 300 sec.⁷⁸ Unfractionated heparin was administered on a weight-adjusted basis to a target ACT > 300 sec with a mean protamine dose of 205 mg (range 15–450 mg).⁷⁸ The primary endpoint of a combined rate of freedom from death, Q-wave MI, repeat coronary revascularization, and stroke were similar for bivalirudin compared with UFH at day 7/discharge (96% bivalirudin vs 94.6% UFH combined endpoint incidence; 1/2/1/0 vs 1/0/1/2 for individual endpoint incidence, respectively), 30 days (93% bivalirudin vs 92.9% UFH, respectively; 2/2/3/0 vs 1/0/1/3, respectively), and 84 days (93% bivalirudin vs 92.9% UFH, respectively; 2/2/3/0 vs 1/0/1/3, respectively).⁷⁸ Interestingly, the rate of stroke was higher in the UFH cohort compared with the bivalirudin cohort at 30 days (5.5% vs 0%, respectively; $P = 0.05$).⁷⁸ Furthermore, although those in the bivalirudin cohort received more PRBC transfusions than the UFH

Table 3 Cardiac surgery trials comparing anticoagulation with bivalirudin vs heparin

Trial	Population (n)	Design	Outcomes	Bival vs UFH; (n, %)	Comparator Arm
Merry <i>et al.</i> ⁷⁷	100, OPCAB	Multicentre randomized	Perioperative blood loss	793 mL vs 805 mL	Yes, UFH
Dyke <i>et al.</i> ⁷⁵ EVOLUTION-ON	98 Bival; 52 UFH, CPB for primary or redo CABG and/or valve	Open label, multicentre, prospective, 2:1 randomized, active-controlled	Freedom from D/MI/S/R at 7 days, 30 days, 12 weeks	95% vs 96%; 95% vs 94%; 95% vs 92%	Yes, UFH
Smedira <i>et al.</i> ⁷⁸ EVOLUTION-OFF	101 Bival; 56 UFH, OPCAB	Open label, multicentre, 2:1 randomized	Freedom from D/MI/R/S at 7 days, 30 days, 12 weeks	96% vs 95%; 93% vs 93%; 93% vs 93%	Yes, UFH
Koster <i>et al.</i> ⁷⁶ CHOOSE-ON	49, HIT (+/?) or anti-PF4/UFH Ab, CPB for primary or redo CABG and/or valve	Open label, multicentre, prospective	Freedom from D/MI/R/S at 7 days, 30 days, 12 weeks	46 (94%) vs * 42 (86%) vs * 40 (82%) vs *	No
Dyke <i>et al.</i> ⁶⁴ CHOOSE-OFF	51, OPCAB in confirmed or previous anti-PF4/UFH Ab or HIT/TS	Open label, multicentre, prospective	Freedom from D/MI/S/R at 7 days, 30 days, 12 weeks	47 (92%) vs * 45 (88%) vs * 45 (88%) vs *	No

Comparator antithrombin cohorts are presented as number (percentage) of each cohort population. * indicates no comparator arm due to a lack of an approved alternative pharmacologic agent in the HIT population. The study by Merry *et al.* described perioperative blood loss and is presented as the median (mL) for each cohort. OPCAB = off-pump coronary artery bypass; Bival = bivalirudin; UFH = unfractionated heparin; CPB = cardiopulmonary bypass; CABG = coronary artery bypass graft surgery; D = death; MI = Q-wave myocardial infarction; S = stroke; R = repeat coronary revascularization; HIT = heparin-induced thrombocytopenia; anti-PF4/UFH Ab = anti-platelet factor 4/heparin antibody; HIT/TS = heparin-induced thrombocytopenia and thrombosis syndrome; ? = suspected.

cohort at day 7 (4.0 vs 2.3; range 1-19 vs 1-16.7, respectively; $P = 0.012$) total postoperative blood loss was similar (median 717 mL vs 783 mL; interquartile range 475-1,190 vs 528-1,032, respectively).⁷⁸ However, the global transfusion rate was observed to be higher in the UFH cohort (58.9% vs 45.5%).⁷⁸

The CHOOSE-ON trial was a multicentre, open-label study with no comparator arm evaluating bivalirudin safety and efficacy in patients undergoing CPB during cardiac surgery (primary/redo CABG, single valve surgery, or CABG with single valve surgery) with confirmed or suspected HIT and (or) a positive anti-PF4/UFH antibody titer.⁷⁶ Confirmed HIT was defined as those patients with both serologic and clinical evidence of the condition.⁷⁶ Suspected HIT was defined as a past diagnosis of HIT with a > 50% drop in platelets from baseline in conjunction with UFH or a positive anti-PF4/UFH antibody titer (≤ 40 days prior to surgery to account for the transient nature of the antibody).⁷⁶ Bivalirudin was administered as a 1 mg·kg⁻¹ bolus followed by a 2.5 mg·kg⁻¹·hr⁻¹ infusion until 15 min before end of surgery.⁷⁶ A 50 mg bolus with a 50 mg·hr⁻¹ infusion of bivalirudin was run concurrently with recirculation to avoid stasis and thrombosis in the closed system while determining whether adequate weaning from the CPB had been achieved and the venous and arterial cannulae could be removed.⁷⁶ The primary endpoint, a combined absence of death, Q-wave MI, repeat coronary revascularization, or stroke at postoperative day

7/discharge (1/0/1/1 for individual endpoint incidence), was observed in 94% of the study population.⁷⁶ The secondary endpoint, the same clinical criteria as the primary endpoint, declined to 86% by postoperative day 30 (3/0/1/1 for individual endpoint incidence) and to 82% by postoperative day 84 (4/0/1/1 for individual endpoint incidence).⁷⁶ Furthermore, intraoperative blood loss increased from a mean estimate of 600 mL to a mean estimate of 1,000 mL for the 24-hr perioperative period (range 100-3,200 mL).⁷⁶ Moreover, the transfusion rate at day 7 was 84%, with platelets (mean of 8.6 ± 7.2 concentrates/patient, range 1-23) being the blood component used most often.⁷⁶ Each transfused patient also received FFP and PRBC (mean of 6.0 ± 4.7 [1-20] and 5.6 ± 3.8 [1-16], respectively).⁷⁶

The CHOOSE-OFF trial was a prospective, multicentre, open-label study with no comparator arm assessing bivalirudin anticoagulation in OPCAB patients with confirmed or prior HIT/thrombotic syndrome (HIT/TS) and/or anti-PF4/UFH antibodies.⁶⁴ Confirmed HIT/TS patients demonstrated evidence of serologic and clinical disease.⁶⁴ Suspected HIT/TS was defined as those patients with circulating anti-PF4/UFH antibody prior to surgery, a platelet count decline of > 50% baseline within 2 weeks of surgery, or a previous episode of HIT/TS.⁶⁴ In this trial, bivalirudin was administered as a 0.75 mg·kg⁻¹ bolus followed by a 1.75 mg·kg⁻¹·hr⁻¹ infusion and monitored with the ACT to a target of ≥ 300 sec.⁶⁴ The primary endpoint of a combined absence of death, MI, stroke, or

repeat revascularization was reported as 92% at postoperative day 7/discharge (0/3/0/1 for individual endpoint incidence).⁶⁴ Interestingly, although there was a reduction in the secondary endpoint (the same clinical criteria as the primary endpoint), the observed rate held steady at 88% at days 30 (0/5/1/1 for individual endpoint incidence) and 84 (0/5/1/1 for individual endpoint incidence) postoperatively.⁶⁴ Furthermore, there were no deaths in the 84-day study period.⁶⁴ Intraoperative blood loss was reported to be a mean of 404 ± 420 mL (range 50–2,140 mL) that increased to a mean of 936 ± 525 mL (range 600–2,745 mL) at 24 hr.⁶⁴ Additionally, PRBC (4.7 ± 5.3 U; range 0–22) was the blood product used most frequently in the 53% of patients requiring a transfusion.⁶⁴ Platelets (10%) and FFP (24%) were also administered to patients (6.5 ± 8.8 U; range 0–22 and 5.8 ± 5.5 U; range 0–20, respectively).⁶⁴

Taken together, the clinical evidence suggests bivalirudin can be a part of a primary or alternative anticoagulant strategy during cardiac surgery with CPB or OPCAB for patients with or without HIT/TS. There appeared to be safety concerns in an observed trend towards increased bleeding in a subset of low-risk patients receiving high-dose bivalirudin in EVOLUTION-ON and CHOOSE-ON. It may be possible that the increased bleeding observed in the first hours after cardiac surgery was impacted by the pharmacokinetics of bivalirudin, i.e., its half-life. Of note in EVOLUTION-ON, there was no difference observed between the bivalirudin and UFH groups in terms of the 24-hr total blood loss. This observation warrants elucidation of the etiology for the observed increase in bleeding

and delineation of bivalirudin dosing and perfusion techniques that may abrogate this risk. Given these data, there is a need for further study to determine the safety and efficacy of bivalirudin in higher-risk patients undergoing repeat, combined, or circulatory arrest operations, those with abnormal renal or hepatic function, and those with preexisting, acquired (low-molecular-weight heparin, GP IIb/IIIa antagonist, clopidogrel), or hereditary (factor V Leiden, prothrombin 20210A gene mutation) abnormalities of the hemostatic system.

Clinical experience with bivalirudin in non-CABG surgery

Clinicians have been expanding the role of bivalirudin from the invasive cardiac revascularization arena to various surgical procedures (Table 4). Bivalirudin has been administered successfully in an adult with HIT undergoing allogeneic heart transplantation.⁷⁹ Furthermore, a recent report described the use of bivalirudin during CPB in a pediatric patient with HIT and thrombosis undergoing orthotopic heart transplant after having undergone an argatroban bridge from the time of veno-arterial extracorporeal circulatory support to transplant.⁸⁰ Moreover, the first patient to receive the HeartMate® II left ventricular assist device was anticoagulated successfully with bivalirudin for eight days in the setting of HIT.⁸¹ In addition, a low-dose continuous bivalirudin infusion (mean 15.2 days, range 7–24 days) was used as a component of the anticoagulation regimen during the temporary implantation of

Table 4 Summary of successful bivalirudin use in the non-CABG setting

Procedure	Patient type	Reference
Allogeneic heart transplant	Adult with HIT	Mann <i>et al.</i> ⁷⁹
Orthotopic heart transplant with CPB	Pediatric with HIT/TS	Almond <i>et al.</i> ⁸⁰
HeartMate® II left ventricular assist device	Adult with HIT	Amir <i>et al.</i> ⁸¹
Temporary total artificial hearts	Adult	Crouch <i>et al.</i> ⁸²
Right atrial masses resection with CPB/ DHCA	Adult with HIT/APS	Leissner <i>et al.</i> ⁸³
Aortic root homograft, left main and right coronary ostia reimplant, SVG bypass graft OMI	Adult with HIT	Wasowicz <i>et al.</i> ⁸⁴
Endovascular abdominal aortic aneurysm repair	Adult	Stamler <i>et al.</i> ⁸⁵
Carotid endarterectomy	Adult with HIT	Finks ⁸⁶
Carotid endarterectomy with CABG	Adult with HIT	Avery <i>et al.</i> ⁸⁷
Femoral-popliteal and femoral-tibial bypass	Adult	Kashyap <i>et al.</i> ⁸⁸
Thromboprophylaxis after orthotopic liver transplantation	Adult with Budd-Chiari syndrome and HIT	Anderegg <i>et al.</i> ⁸⁹

CABG = coronary artery bypass graft surgery; HIT = heparin-induced thrombocytopenia; CPB = cardiopulmonary bypass; HIT/TS = heparin-induced thrombocytopenia and thrombosis syndrome; DHCA = deep hypothermic circulatory arrest; APS = antiphospholipid syndrome; SVG = saphenous vein graft; OMI = obtuse marginal 1.

total artificial hearts.⁸² Bivalirudin was also utilized recently to manage the resection of right atrial masses in a patient with HIT and antiphospholipid syndrome undergoing CPB involving deep hypothermic circulatory arrest.⁸³ Bivalirudin has additionally been shown to have a favourable outcome in a patient with HIT undergoing a complex procedure with CPB involving urgent redo aortic root homograft placement with saphenous vein bypass grafting.⁸⁴

The scope of bivalirudin has broadened further to encompass procedures for the management of thoracic aorta, carotid artery, and femoral artery pathologies. When compared with UFH, bivalirudin has demonstrated a lower total complication rate in patients having endovascular abdominal aortic aneurysm repair.⁸⁵ Furthermore, patients with HIT undergoing carotid endarterectomy or a combination of carotid endarterectomy and CABG have been anticoagulated effectively with bivalirudin.^{86,87} Additionally, a recent study demonstrated the use of bivalirudin for anticoagulation during femoral-popliteal and femoral-tibial bypass surgery.⁸⁸ In keeping with the widening clinical experience, an intriguing report demonstrated successful thromboprophylaxis with bivalirudin following orthotopic liver transplantation in a patient with Budd-Chiari syndrome and HIT.⁸⁹

Within the previous two decades, bivalirudin has emerged as an alternative anticoagulant to UFH in various settings and ongoing studies continue to expand its role. Potential future clinical uses of bivalirudin may include its use as a component of saphenous vein graft flush solutions, inpatient deep vein thrombosis/pulmonary embolism thromboprophylaxis parenteral-to-oral anticoagulation bridge, atrial fibrillation parenteral-to-oral anticoagulation bridge, treatment for cerebral venous sinus thrombosis as well as hypercoagulable states, i.e., neoplasm-associated thrombosis and disseminated intravascular coagulation.

Potential of bivalirudin-mediated vascular graft patency

Increasing evidence suggests bivalirudin-mediated anticoagulation augments angiographically quantifiable vessel patency and graft flow in vessels surgically anastomosed to bypass coronary obstructions.^{77,90} This observation can be attributed to a multitude of studies describing thrombin's role in vascular smooth muscle cell (SMC) proliferation,⁹¹ migration,⁹² inflammation,⁹³ and fibrosis,⁹⁴ and attenuation of neointimal hyperplasia after arterial injury with hirudin administration.⁹⁵⁻⁹⁷ Thrombin mediates SMC proliferation and migration mainly via the protease-activated receptor 1⁹¹ and, in part, by protease-activated receptor 4⁹⁸ in this cell type. Downstream cell signalling by these thrombin-

activated G-protein coupled receptors upregulate a slew of immediate-early genes (*egr-1*, *c-fos*, *c-jun*, *junB*, *FosB*, *fra-1*)^{99,100} as well as transcription factors (nuclear factor of activated T cells,^{101,102} cAMP response element binding protein,¹⁰³ and neuron-derived orphan receptor-1)¹⁰⁴ to translate thrombin's mitogenic effect onto vascular SMCs. Moreover, thrombin modulates an inflammatory and fibrotic response from vascular SMCs by augmenting interleukin-6, monocyte chemotactic protein-1, and collagen production.^{93,94} Interestingly, thrombin may be involved in a self-perpetuating feedback loop whereby SMCs undergo apoptosis after disruption of vascular integrity¹⁰⁵ exposing phosphatidylserine among other cell membrane components that potentiate the creation of the prothrombinase complex and hence thrombin.¹⁰⁶ Taken together, it is reasonable to consider that attenuating thrombin-mediated neointimal hyperplasia via direct thrombin inhibition by bivalirudin may lead, in part, to a reduction in graft restenosis.

The potential biologic mechanisms related to graft patency need further evaluation in long-term trials examining graft patency rates. The answer may add yet another reason for increasing bivalirudin use during CABG to reduce the graft restenosis-revascularization scenario commonplace with UFH anticoagulation. Further, it may be possible that a drug-eluting stent carrying bivalirudin (at a molar concentration incapable of systemic anticoagulation) could serve as a vehicle to deliver sustained, localized thrombin antagonism to biologically and mechanically abrogate the SMC proliferation that occurs after vascular conduit grafting.

Future considerations

Cardiac surgery has seen steady progress with respect to surgical and perfusion techniques, particularly with CPB. Unfractionated heparin has been the central anticoagulant used by cardiac anesthesiologists to significantly reduce thrombosis *in situ* and in the CPB circuit, but it has well documented limitations with potentially devastating consequences. Unfractionated heparin has not been readily replaced because of its active reversing agent, protamine, and for lack of a better anticoagulant. Recently, with the need to address the HIT population undergoing surgical or percutaneous coronary revascularization therapy, anticoagulation achieved with bivalirudin demonstrated non-inferior clinical outcomes compared to UFH in small, underpowered studies. However, lacking active reversibility, bivalirudin has not been adopted as the anticoagulant of choice during cardiac surgery despite its short half-life which allows for quick clearance in most patients and its incorporation into the 2008 American College of Chest Physicians guidelines for HIT management.¹⁰⁷

Table 5 Blood stasis-limiting strategies in CPB circuit and surgical field during cardiac surgery with bivalirudin

Use of closed systems
Shunting line from arterial filter to cardiotomy reservoir
Intermittent compression of the collapse venous reservoir with flushing back in the hard shell cardiotomy reservoir to provide flow of systemic blood in the cardiotomy reservoir and to maintain bivalirudin levels
Storage of excess blood in citrated bags instead of hard shell cardiotomy reservoir
Processing excess blood with cell saver
Minimize use of cardiotomy suction; use cell saver to avoid aspiration and systemic infusion of “activated” blood from the operative field
Replace blood cardioplegia with crystalloid cardioplegia

CPB = cardiopulmonary bypass. Modified from Koster *et al.* J Thorac Cardiovasc Surg 2005; 129: 1391-4 and Ann Thorac Surg 2007; 83: 572-7.

With the advent of next generation anti-platelet therapy (i.e., irreversible P2Y₁₂ inhibitor, prasugrel; reversible P2Y₁₂ inhibitors, cangrelor and ticagrelor; and platelet thrombin receptor antagonist, SCH 530348) on the horizon, unanswered questions remain regarding the appropriate anti-platelet regimen to employ given bivalirudin's anti-platelet effect.¹⁸ In order to mitigate perioperative bleeding, should anti-platelet medications and/or aspirin be continued or discontinued when bivalirudin use is anticipated? What is the optimal bivalirudin dose and period of treatment if there is a potential for a rebound phenomena whereby anti-platelet medication discontinuation leads to increased platelet reactivity and thereby thrombosis? And interestingly, can bivalirudin be used as an anti-platelet and anticoagulant “bridge” prior to cardiac surgery when an anti-platelet agent is discontinued?

Given the ambiguity for reliable point-of-care monitoring, large controlled randomized trials are required to investigate the most reliable monitoring technology for bivalirudin-mediated anticoagulation. Moreover, although a protocol to administer bivalirudin during CPB has been developed to address points of stagnant blood flow,^{31,108} what perfusion techniques can be developed to further improve bivalirudin's efficacy as an anticoagulant at points of fluid stasis in the CPB circuit (Table 5)?

Bivalirudin will continue to be part of the pharmacologic armamentarium for patients with HIT undergoing cardiac surgery. Further, large population, multicentre, randomized, controlled, double-blind studies and more extensive clinical experience are required before bivalirudin can potentially unseat UFH and attain an equal anticoagulant status in the cardiac surgical setting.

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